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CONSEQUENCES OF INADEQUATE USE OF GLUCOSE LOWERING DRUGS AND ASSOCIATED RISK FACTORS

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my lovely children Olivia, Malin and Conrad

“There are only two days in the year that nothing can be done.
One is called Yesterday and the other is called Tomorrow. Today
is the right day to Love, Believe, Do and mostly Live.”

Dalai Lama XIV

ABSTRACT

Diabetes Mellitus is characterized by chronically elevated blood glucose levels, hyperglycaemia. Consistent adherence to appropriate glucose-lowering drug therapy is fundamental to prevent disease progression, diabetes-related complications and premature death. If patients do not dispense, do not take their medication, or if the drugs are not prescribed according to evidence-based medicine, the consequences may be serious. The purpose of this thesis was to study acute consequences of inadequate use of glucose-lowering drugs, and its associated risk factors.

In **Study I** the impact of symptomatic hypoglycaemia on medication adherence, patient satisfaction with treatment, and glycaemic control was studied in patients with type 2 diabetes treated with metformin and SU. The main finding was that adherence was negatively associated with the severity of the experienced hypoglycaemic symptoms. Despite poorer adherence to glucose-lowering drugs, the group with more severe hypoglycaemia showed better glycaemic control compared to the group with milder symptoms. The results suggest that glycaemic control is achieved at the expense of symptoms of hypoglycaemia in patients treated with metformin and SU. Dissatisfaction with medicine and barriers to medication adherence were more likely among patients with more severe hypoglycaemia. The study shows that only 40 % of the patients treated with metformin and SU in a primary care setting achieved the HbA1c target. Hypoglycaemia seems to refrain both patients and physicians from adherence to the best possible use of glucose lowering drugs.

In **Study II**, potential risk factors associated with fatal hyperglycaemia were studied in deceased individuals with dispensed glucose-lowering drugs from pharmacies and their matched living controls. A significantly larger proportion of those who died due to hyperglycaemia lived in single households, had a history of psychiatric illness, was treated with insulin and had known alcohol abuse as compared to controls. Highly elevated glucose levels ($\text{HbA1c} \geq 75 \text{ mmol / mol}$) at the last health care visit were significantly associated with an increased risk of fatal hyperglycaemia. A larger proportion of the deceased had unsatisfactory refill adherence of glucose-lowering drugs. In addition, we found that 48 (15%) of the deceased individuals were undiagnosed.

In **Study III**, reference concentrations for fatal metformin intoxications and associated risk factors were studied in a nationwide group of deceased, with detected metformin in the blood. The extensive information from forensic autopsy results and police reports was supplemented with detailed information on medical history, dispensed drugs and diabetes-related variables from several linked national registries. The verified reference concentrations for metformin may be particularly useful in cases where complementary information is missing. Metformin intoxication was intentional only in eight cases (23%), suggesting that high drug concentrations in the post-mortem context may not always be due to an acute high intake of the drug. The study shows that the most common risk factor in metformin intoxications was contraindications to the use of metformin, including; alcohol abuse and renal dysfunction. In this study, less than half of the study population achieved the recommended HbA1c target, based on the treatment goals listed in the national guidelines.

Conclusions: The results confirm that high blood glucose levels need clinical attention, as an indication of inadequate use of glucose lowering drugs, which may lead to serious consequences. Further, unsatisfied refill adherence of GLD is associated with fatal hyperglycaemia in individuals with diabetes. Increased understanding of patient-reported

outcome measures could improve the care of individuals with diabetes mellitus. The results also indicate that socio-economic and psychosocial factors, e.g. single households and / or alcohol abuse, should be noted as they may be important risk factors that seemingly are equally important as traditional risk factors. The included studies collectively indicate that both patient behaviour and the physician's clinical inertia represent crucial barriers to appropriate use of glucose lowering drugs.

Finally, by linking forensic toxicology data with national registries, we have revealed results of importance to improve adequate use of glucose lowering drugs and which may contribute to prevent patients from severe consequences due to inadequate use of glucose lowering drugs. This thesis demonstrates a public health-oriented application of medico-legal autopsies results, beyond their immediate and isolated use in forensic medicine.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following studies, which will be referred to by their roman numerals.

- I. **Walz L**, Pettersson B, Rosenqvist U, Deleskog A, Journath G, Wändell P. Impact of symptomatic hypoglycaemia on medication adherence, patient satisfaction with treatment, and glycaemic control in patients with type 2 diabetes. *Patient Prefer Adherence* 2014 Apr 30; 8:593-601
- II. **Walz L**, Jönsson AK, Zilg B, Östgren CJ, Druid H. Risk factors for fatal hyperglycaemia confirmed by forensic post-mortem examination - A nationwide cohort in Sweden. *PLos One* 2016 Oct21;11(10)
- III. **Walz L**, Jönsson AK, Ahlner J, Östgren CJ, Druid H. Metformin - Post-mortem fatal and non-fatal reference concentrations in femoral blood and risk factors associated with fatal intoxications. *Manuscript Submitted*

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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical group
BMI	Body Mass Index
CI	Confidence Interval
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
eGFR	Estimated Glomerular Filtration Rate
GLD	Glucose-Lowering Drugs (GLD).
HbA1c	Glycosylated Haemoglobin A1c
HR	Hazard Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems - Tenth Revision
LISA	Longitudinal integration database for health insurance and labour market studies
MeSH	Medical Subject Headings
NBHW	The National Board of Health and Welfare
NDR	the Swedish National Diabetes Registry
NFMD	National Forensic Medicine Database
OR	Odds Ratio
PIN	Personal Identification Number
PROM	Patient Report Outcomes Measures
SD	Standard Deviation
SPC	Summary of Product Characteristics
SPDR	The Swedish Prescribed Drug Registry
SU	Sulfonylurea
T1DM	Type 1 diabetes Mellitus
T2DM	Type 2 diabetes Mellitus
TSQM	Treatment Satisfaction Questionnaire for Medication
VG	Vitreous Glucose
WHO	World Health Organisation

1 POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Diabetes mellitus är en av världens vanligaste och snabbast ökande kroniska sjukdomar. Sjukdomen kännetecknas av kroniskt förhöjda blodglukosvärden, hyperglykemi. Kontinuerlig följsamhet till lämplig glukossänkande läkemedelsbehandling i syfte att uppnå glukoskontroll är en grundläggande del av behandlingen för att förhindra sjukdomsprogression, diabetesrelaterade komplikationer och prematur död. Men om patienten inte hämtar ut, inte tar sina läkemedel eller om läkemedlen inte förskrivs enligt etablerad praxis kan konsekvenserna bli förödande. Syftet med denna avhandling har varit att studera konsekvenser av inadekvat användning av glukossänkande läkemedel, och dess associerade riskfaktorer. De inkluderade studierna fokuserar på akuta komplikationer som kan vara associerade med inadekvat användning av glukossänkande läkemedelsbehandling, såsom *symptomatisk hypoglykemi*, *dödlig hyperglykemi* och *metformin-förgiftning* med dödlig utgång.

I **studie I** undersöktes om *symptomatisk hypoglykemi* påverkar följsamheten till ordinerad glukossänkande läkemedelsbehandling, patientens nöjdhet med behandlingen och den glykemiska kontrollen hos patienter med typ 2 diabetes. En ökande svårighetsgrad av de upplevda hypoglykemierna var associerad med en försämrad följsamhet till den glukossänkande läkemedelsbehandlingen. Trots sämre följsamhet till glukossänkande läkemedel var gruppen med mer besvärande hypoglykemi förknippad med bättre glykemisk kontroll. Resultaten tyder på att glykemisk kontroll uppnåddes på bekostnad av biverkningar, såsom symptomatisk hypoglykemi, hos patienter som behandlas med metformin och SU. Patientrapporterade utfallsmått visade att en större andel av de med mer besvärande hypoglykemi var mera missnöjda med sin glukossänkande behandling samt uppgav fler barriärer för god följsamhet till läkemedelsbehandlingen jämfört med de som upplevde mindre besvärande symptom. Studien åskådliggör även att endast 40 % av patienterna som behandlades med metformin och SU uppnådde målet för HbA1c baserat på de behandlingsmål som angavs i de svenska nationella riktlinjerna.

I **studie II** undersöktes möjliga riskfaktorer associerade med *dödlig hyperglykemi* hos avlidna individer som hämtat ut glukossänkande läkemedel på apotek och dess matchade levande kontroller, slumpmässigt utvalda i läkemedelsregistret. En signifikant större andel av de som avled i dödlig hyperglykemi levde i ensamhushåll, behandlades med insulin och hade känt alkoholmissbruk jämfört med kontrollerna. Kraftigt förhöjda glukosvärden ($\text{HbA1c} \geq 75 \text{ mmol/mol}$) vid senaste sjukvårdsbesöket var associerat med en ökad risk att dö i hyperglykemi. De som dog av hyperglykemi uppvisade i större grad perioder (> 125 dagar) då de saknade uthämtade glukossänkande läkemedel än kontrollerna. Polisrapporterna bekräftade att ca hälften av de avlidna inte hade några glukossänkande läkemedel på platsen vid dödstillfället. Dessutom fann vi att 48 (15 %) av de avlidna individerna var odiagnostiserade och hade aldrig hämtat ut glukossänkande läkemedel på apotek. Resultatet bekräftar att många individer med typ 2 diabetes förmodligen är odiagnostiserade och att fatal hyperglykemi kan vara den första manifestationen av diabetes.

I **studie III** studerades riskfaktorer associerade med dödlig *metformin-förgiftning* i en rikstäckande grupp avlidna individer med metformin i blodet. Koncentrationen av metformin i lårblod var signifikant högre hos dem som dött av metformin-förgiftning jämfört med

kontrollerna. Den omfattande informationen från medicinska obduktionsresultat och polisrapporter kompletterades med betydande information om sjukdomshistoria, uthämtade läkemedel och diabetesrelaterade variabler från flera länkade nationella register. De verifierade referenskoncentrationerna för metformin kan komma att bli särskilt användbara i fall där komplementär information saknas. I endast åtta fall (23 %) var metformin-förgiftningen avsiktlig, vilket talar för att de flesta dödsfallen snarare orsakats av en ackumulering av läkemedlet över tid. Studien visar att den vanligaste riskfaktorn vid metformin-förgiftning var kontraindikationer för användningen av metformin, kvantifierad som; alkoholmissbruk (77,3%), nedsatt njurfunktion (40,9%), svår pågående infektion (27,7%) eller intorkning (31,6%). I den här studien uppnådde mindre än hälften av studiepopulationen det rekommenderade HbA1c-målet enligt den sista registreringen i det nationella diabetesregistret.

Sammanfattande slutsats: Ett led i att förbättra omhändertagandet av individer med diabetes kan vara att uppmärksamma inadekvat glukossänkande behandling för att möjliggöra optimering av behandlingen. Avhandlingen visar att konsekvenserna av inadekvat användning av glukossänkande läkemedel är mångfacetterade. Alla tre studierna i avhandlingen visar dock att den glykemiska kontrollen var otillräcklig hos en stor andel av de som drabbades av akuta allvarliga komplikationer associerade med inadekvat läkemedelsanvändning. Studie II åskådliggör att bristande uttagsföljsamhet är associerat med dödlig hyperglykemi hos individer med diabetes. Resultaten bekräftar att höga blodglukosvärden borde uppmärksammas mer i klinisk vardag eftersom det kan vara tecken på non-adherence eller annan inadekvat läkemedelsanvändning, som kan leda till allvarliga konsekvenser och i värsta fall dödlig hyperglykemi. Patienter som rapporterar missnöje med sin behandling bör tas på allvar då missnöjet kan vara associerat med låg följsamhet och ökad risk för avbruten behandling med allvarliga konsekvenser för patienten, vården och samhället. Ökad förståelse för patient-rapporterade utfallsmått skulle kunna förbättra omhändertagandet av individer med diabetes mellitus. Resultaten från studie II och III indikerar dessutom att socioekonomiska och psykosociala faktorer, t.ex. ensamhushåll och/eller med alkoholmissbruk, borde uppmärksammas då de kan vara viktiga riskfaktorer som åsidosätts för mer traditionella riskfaktorer. Samtliga studier i avhandlingen pekar på att både patientens och sjukvårdspersonalens handlande utgör viktiga barriärer för att uppnå god följsamhet till lämplig glukossänkande läkemedelsbehandling.

Slutligen visar avhandlingen värdet av medicinska/rättskemiska undersökningsresultat, utöver deras omedelbara och isolerade användning i rättsmedicin. Studiernas resultat kan vara av värde för framtida forskning för att studera lämpliga interventioner för att förbättra användningen av glukossänkande läkemedel i de identifierade riskgrupperna.

2 INTRODUCTION

Pharmaceutical drugs are of great benefit to patients to cure and relieve symptoms, delay complications or prevent premature death. However, medicines do not work if they are not taken or they may have negative consequences if not used according to evidence-based medicine. Findings collectively suggest that inadequate use of medications, including poor adherence and non-persistence with prescribed treatment regimens, reduces the effectiveness of medicine which increases morbidity and premature death, as well as increasing healthcare expenditures [1-4]. Adherence to appropriate prescribed medication helps patients stay healthy and correlates with a better quality of life as well as reduced cost for society [5-8]. Nevertheless, physicians should not assume that patients fully adhere to treatment regimens even if the consequences of non-adherence may be harmful. In view of that, physicians and other healthcare providers do not have sufficient control over the effectiveness of the prescribed treatment regimens. Several studies have shown that there are in general more adherence issues in long-term treatment plans regarding asymptomatic chronic diseases such as diabetes mellitus and those prescribed preventive medicine, than in treatment for acute diseases [8-10].

The global prevalence of diabetes mellitus is on the rise and uncontrolled diabetes is a common cause of death; in 2015 diabetes caused approximately 5 million deaths globally [11]. Patients with diabetes are characterised by chronic hyperglycaemia. Accordingly, adequate management of glucose-lowering drugs (GLD) with regular adherence to medicine is crucial to prevent disease progression, diabetes-related complications and delay premature death. However, several systematic reviews over recent years mutually highlight non-adherence to GLD as a prominent and ongoing serious problem [12-16]. Besides, approximately 600 individuals die each year in Sweden due to the consequences of intentional or accidental inadequate use of pharmaceutical drugs [17]. The World Health Organization has previously stressed that focusing on improvement of adherence to medicine could add more value to patients, society and the global wellbeing than any new medical discovery [8].

The overall rationale behind this thesis is that inadequate use of medicine, including poor adherence, causes serious consequences for patients and for public health and society. This thesis focuses on non-adherence to GLD, since diabetes mellitus is a common chronic disease where non-adherence could result in serious and even life-threatening consequences for affected patients [18-20]. Further, the use of GLD in Sweden has escalated over recent years; the underlying explanations are probably an ageing population and earlier initiation of treatment, which calls for an increased awareness of inadequate use of GLD [21-24]. Medication non-adherence may be considered as a modifiable disorder. However, most healthcare providers are not aware of the magnitude of the problem and usually not skilled to identify or handle medication non-adherence. The full benefit of treatment can only be achieved if the patient is diagnosed at the right time, treated with the right dose, with an effective drug with respect to the diagnosis and if patients follow prescribed treatment regimens reasonably carefully. Therefore, both patient behaviour and the physician's clinical

inertia may represent possible barriers to adequate use of medicine. Considering the large amount of GLD that are available, understanding and addressing patient adherence problems and the physician's clinical inertia are important to optimise treatment with pharmaceuticals and improve glucose control and the patient's health outcomes.

This thesis aims to reveal information that may lead to awareness and better understanding of the factors behind inadequate use of medicine to effectively optimise the use of GLD and improve the patient's health outcomes.



3 BACKGROUND

3.1 DIABETES

3.1.1 Epidemiology

Diabetes mellitus is one of the most common and fastest growing chronic diseases in the world. The WHO reports that 422 million adults were diagnosed with diabetes in 2014 compared to 108 million in 1980 [25]. The prevalence of diabetes has more than doubled over recent decades and it has been estimate that 592 million individuals (10%) of the total adult population will suffer from diabetes by 2035 [26]. Diabetes type 2 (T2DM) is the most common form, accounting for 85-95% of all cases. This form of diabetes may remain undetected for many years, adding a massive number of people living with undiagnosed T2DM [26, 27]. The largest increase in T2DM is perceived in low- and middle-income countries and the increase in incidence of T2DM is probably due to unhealthy lifestyle factors. However, western countries, including Sweden, are experiencing a plateau in the incidence of T2DM [25].

Prevalence of diabetes is apparently lower in Scandinavia than other countries [26]. The prevalence of diabetes mellitus in Sweden is approximately 4-6.8%, with a very high proportion of T2DM (85-90%) [23, 28-30]. The prevalence of diabetes in a population is strongly dependent on age. In Sweden almost 20% of individuals 80 years of age or older are diagnosed with diabetes [23]. Furthermore, studies consistently report a larger proportion of men versus women with diabetes [21-23, 29, 31]. The prevalence of adults with T2DM treated with GLD in Sweden has increased in recent years; the underlying explanations are probably an ageing population and earlier initiation of treatment [23, 30]. The overall incidence seems to be stable but even when assuming constant incidence, Anderson et al. estimate prevalence of diabetes to be 10.4% by 2050 in Sweden [29].

To conclude, diabetes mellitus is expected to become one of the most common health problems in Sweden and more than half a million people will be treated with GLD in the near future. This doctoral thesis aims to evaluate consequences of inadequate use of GLD and contribute to a better understanding and awareness of risk factors associated with these consequences to improve future outcomes.

3.1.2 Classification

Diabetes mellitus is a cluster of complex metabolic diseases with raised blood glucose levels due to impairment in insulin secretory function or where cells do not respond accurately to the insulin produced. The classification is based on older recommendations from World Health Organization (WHO) but there are also and updated versions from American Diabetes Association ADA [32, 33]. According to current recommendations, most individuals with diabetes can be classified into the following general categories based on etiology [32].

Type 1 diabetes accounts for the vast majority of diabetes in children but represents only 5–10% of the total population with diabetes. T1DM usually starts early in life, although an individual can develop the disease at any age. This type of the disease is a multifactorial disease with genetic predisposition and environmental factors that trigger an autoimmune

impairment of the pancreas, where the β -cells destruction leads to a total stop in insulin production. **Latent adult autoimmune diabetes, LADA** is a slow progressing type of type 1 diabetes. Patients resemble T2DM with conserved β -cell function, without the urgent need for insulin therapy but with the presence of autoantibodies directed to insulin-producing cells [34].

Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes. T2DM is a progressive disease with worsening hyperglycaemia over time, due to a progressive loss of insulin secretion as well as insulin resistance. Studies have shown that a genetic predisposition increases the risk in the presence of environmental factors such as high calorie nutrition, an inactive lifestyle and use of tobacco [35, 36]. During earlier stages, the symptoms of hyperglycaemia could be asymptomatic or not severe enough to alert the patient [37]. Nevertheless, these patients are at increased risk of developing severe diabetes-related complications.

Gestational diabetes mellitus (GDM) is a temporary disease diagnosed in the second or third trimester of pregnancy. It is important to regularly monitor glucose levels among women with previous gestational diabetes, since they have an increased risk of developing type 2 diabetes compared with women with normoglycemic pregnancy [38].

Specific types of diabetes due to other causes:

- Monogenic diabetes syndrome (MODY) is a form of neonatal diabetes with a genetic defect of β -cells function; a minor fragment of patients with diabetes (<5%)
- Cystic fibrosis–related diabetes (CFRD) is a comorbidity in people with cystic fibrosis, with insulin deficiency as the primary defect
- Drug- or chemical-induced diabetes
- New-onset diabetes after transplantation (NODAT); in individuals who develop diabetes post organ transplantation
- Pancreatic disease including surgical removal
- Endocrinopathies (Cushing's syndrome)
- Rare genetic disorders (e.g. Klinefelter's syndrome)

3.1.3 Glucose metabolism

Energy is required for the functioning of the organs in the body. Most tissues can use fat or protein as an energy source, but the brain can only use glucose. Accordingly, carbohydrates, mainly available as glucose, are the primary energy source. The concentration of glucose in plasma should normally be lower than 100 to 109 mg per decilitre (5.55 to 6.05 mmol/L) in healthy individuals [32]. In the case of increased concentrations of glucose, liver and muscle cells convert excess glucose to glycogen. The liver is a central storage site for glycogen [39]. Glycogen is mobilised and broken down to glucose by gluconeogenesis when the blood glucose concentration is low, or the cells need energy. When oxygen is available, glucose is metabolized to substantial amount of energy and carbon dioxide and water. In the absence of oxygen, the metabolism becomes incomplete, less energy is produced and lactic acid is formed. After food intake insulin is released via the incretin effect, due to the increased blood sugar level. The uptake of glucose in the skeletal muscle cells, adipose tissue and the release of glucose from glycogen is regulated by insulin. Insulin and glucagon work synergistically to keep blood glucose concentrations normal and they are secreted from the endocrine tissue in the pancreas [39]. The endocrine tissue is grouped in the islets of Langerhans and consists of different cell types with different functions. The α -cells produce glucagon and β -cells produce proinsulin, which is converted to insulin in the circulation [40, 41].

3.1.4 Complications

Poorly controlled diabetes has dreadful consequences for patients, clinicians and society. There are different types of diabetes-related complications, acute and chronic conditions. In this thesis focus is on the acute complications, including diabetes coma, hyperglycaemia, hypoglycaemia, and intoxications due to GLD. Further, chronic complications are divided into micro- and macrovascular complications, with a wide range of different conditions. Microvascular complications are complications of the small blood vessels of the body and include neuropathy, retinopathy and nephropathy, which may lead to foot ulcers, limb amputation, blindness and renal failure. Macrovascular complications are complications of the large blood vessels of the body, including the coronary arteries, the aorta, and the sizeable arteries in the brain and in the limbs. The most important macrovascular complication is cardiovascular disease (CVD), including stroke and myocardial infarction (MI). The ultimate goal of type 2 diabetes management is to prevent or delay the onset of diabetes-related micro- and macrovascular complications. The main focus of treatment lies in controlling HbA1c, but control of other cardiovascular risk factors such as obesity, hypertension and dyslipidaemia are also important. Several landmark studies have showed that uncontrolled blood glucose is related to disease progression and microvascular complications, though the impact of hyperglycaemia on macrovascular complications still remains slightly vague [42-45]. Nonetheless, the 10-year follow-up of the UKPDS study shows strong evidence that tight glycaemic control not only reduces microvascular complications but also macrovascular complications such as myocardial infarction and all-cause mortality [46]. The risk of severe cardiovascular complications is more than doubled in patients with T2DM compared to the general population [47, 48]. However, the incidence and risk of macrovascular morbidity and all-cause mortality has decreased substantially both in patients with diabetes and in the general population over the last two decades [49]. Research results collectively emphasise the importance of improved glycaemic control and progressive multifactorial risk reduction in

patients with T2DM to delay or prevent diabetes-related complications and premature death [50-53].

3.1.5 Diagnosis

Diabetes is a complex variety of diseases but with chronic elevated plasma glucose levels in common. Accordingly, diabetes may be identified based on plasma glucose criteria; either by the fasting plasma glucose (FPG) value or by the oral glucose tolerance test (OGTT) [32]. The diagnosis requires a fasting plasma glucose $\geq 7\text{mmol/L}$ or a 2-hour venous glucose over $\geq 11.1\text{mmol/L}$ (after an oral glucose load of 75 g), alternatively a random venous plasma glucose $\geq 11.1\text{mmol/L}$, if there are simultaneous symptoms of hyperglycaemia [33, 54].

The diagnosis can also be made by measuring HbA1c. The HbA1c is a marker of the average blood glucose levels over the previous 4-6 weeks, [55]. This method does not require fasting and is more convenient compared with the FPG and OGTT. These benefits may be balanced by lower sensitivity, increased cost, limited availability of HbA1c testing in parts of the developing world, and the poor association between HbA1c and average glucose in some patients [54, 56].

If the patient has symptoms of hyperglycaemia, the diagnosis of diabetes requires only one single randomised plasma glucose test. If no symptoms are present, two consecutive tests are required for diagnosis.

Table 1. Presents diagnostic limit values for diabetes.

	Plasma Glucose		HbA1c
	Venous	Capillary	
Fasting Plasma Glucose	$\geq 7\text{mmol/L}$	$\geq 7\text{mmol/L}$	
Oral Glucose Tolerance	$\geq 11.1\text{mmol/L}$	$\geq 12.2\text{mmol/L}$	
Random Plasma Glucose	$\geq 11.1\text{mmol/L}$	$\geq 12.2\text{mmol/L}$	
HbA1c			$\geq 48\text{mmol/mol}$

Normally, FPG, OGTT and HbA1c could all be used to diagnose diabetes. However, one method only is not sufficient to identify the diagnosis of diabetes in every individual therefore the diagnostic methods do not replace each other but partly identify different groups with elevated plasma glucose.

3.1.6 Treatment

Lifestyle intervention is the basis for treatment of type 2 diabetes, but pharmacological treatment of hyperglycaemia is needed in most patients sooner or later due to the progressive nature of the disease.

Glucose-lowering drugs

Today, there are a variety of drugs that lower blood glucose with different mechanisms of action. For optimal drug selection, the prescriber should consider factors that the individual can influence (attitude, treatment compliance and support from relatives) but also factors that the individual cannot influence (age, expected short life, other severe chronic disease and cardiovascular disease). In addition to this, other factors such as obesity, long diabetic duration, renal dysfunction, risk of hypoglycaemia and price are also crucial for drug selection to optimise treatment [51]. The number of GLD classes has increased over the past two decades. An overview of the most commonly used drugs for diabetes mellitus are given below.

Biguanides (metformin) lowers blood glucose levels primarily by decreasing the amount of glucose produced by the liver. Metformin also helps to lower blood glucose levels by making muscle tissue more sensitive to insulin. Recent evidence suggests that metformin has some glucose-lowering action directly via the intestine, it does not lead to hypoglycaemia and is considered to be weight neutral [57].

Sulfonylurea (SU) stimulates the β -cells of the pancreas to release more insulin. There is concern that this class of drugs may overwork the pancreas, thereby speeding up the progression of type 2 diabetes. The risk of weight gain and hypoglycaemia is increased in patients treated with sulfonylurea [58].

Glitazones lower the level of blood sugar and affect the fat cells to increase sensitivity to insulin. However, the maximum effect will come after 2-3 months. The drug is therefore rarely suitable for monotherapy if the purpose of the treatment is rapid HbA1c reduction. Pioglitazone should not be used in heart failure. The drug is associated with weight gain [59].

Alpha-glucosidase inhibitors inhibit carbohydrate uptake from the intestine to the blood. Since more carbohydrates remain in the gut, the incidence of gastrointestinal side-effects is high. This class does not produce hypoglycaemia. The high incidence of gastrointestinal side-effects and the modest effect on HbA1c limit the use of the drug [58].

Incretin-based drugs

After food intake, the hormone incretin is formed in the intestine which affects the pancreas. The hormone causes the pancreas to increase insulin production and provides a faster sense of satiety [60]. This stimulation occurs through a glucose-dependent mechanism, which causes the insulin release to stop if blood glucose drops below 5 mmol/l. Incretin treatment is divided into GLP-1 agonists (subcutaneous injection treatment) and DPP-4 (dipeptidyl peptidase-4) inhibitors [60].

GLP-1 agonists: GLP-1 is a hormone produced in the small intestine that stimulates insulin secretion and inhibits glucagon secretion, thereby lowering blood sugar. Shorter-acting agonists of the GLP-1 receptor are particularly effective at lowering post-meal glucose peaks, whereas longer-acting GLP-1 agonists have more balanced effects on lowering post-meal and fasting glucose levels. GLP-1 agonists improve the glycaemic control without causing hypoglycaemia and may also result in weight loss [60].

DPP-4 inhibitors: GLP-1 is inactivated in the blood by the enzyme dipeptidyl peptidase-4. When the glucose levels are elevated, the activity of the DPP4-inhibitor increases levels of GLP-1, which stimulates insulin production and decreases production of glucagon. DPP-4 inhibitors improve the glycaemic control without causing hypoglycaemia and are generally weight-neutral, although modest weight loss has been observed [61].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the most recently introduced group of GLD; the glucose-lowering effect is induced by increased glucose secretion in the urine. Glucose in the bloodstream passes through the kidneys, where the glucose can be excreted or reabsorbed. SGLT2 work in the kidney to reabsorb glucose, and the SGLT2 inhibitors block this action and glucose will be eliminated with the urine. Because of the increased glucose levels in the urine, side-effects can include urinary tract and yeast infections [59, 62]. The effect of these drugs is independent of insulin resistance and beta cell failure, therefore a similar HbA1c-lowering effect is seen in the onset of type 2 diabetes as in long-term diabetes. Other beneficial effects of treatment with SGLT2 inhibitors may be a slight weight reduction. However, the glucose-lowering effect decreases with renal impairment (eGFR <45 ml/min) [51].

Oral combination therapy: Because the drugs listed above act in different ways to lower blood glucose levels, they may be used together. Combination therapy is designed to improve efficacy; switching from one single drug to another is not as effective as adding another type of glucose-lowering drug.

Insulin is a hormone produced by the pancreas that stimulates cells in the body to remove glucose from the blood for storage or use. Normally, insulin is released when the body has high amounts of sugar in the blood, such as after a meal, to bring levels back into a normal range. Today there are a large number of different insulin regimens. Commonly a morning injection of long-acting or intermediate-acting insulin is given but administration at bedtime may also be necessary. There is also short-acting insulin usually administered with meals [63]. Treatment with insulin in type 2 diabetes is superior if there is a need for rapid glucose lowering or in case of pronounced beta cell failure. Similarly, insulin can be used if there is contraindication to other GLD. Insulin treatment increases the risk for hypoglycaemia and risk for weight gain.

3.1.7 Treatment goals

Glycaemic control minimises the risk of developing complications. Therefore reasonably priced, safe and efficient GLD are essential for the survival of individuals with diabetes. Guidelines propose intensive glucose-lowering treatment, preferably with metformin, at or just after diagnosis [53, 64, 65]. Sweden has national guidelines that recommend a target level of HbA1c of less than 53mmol/mol, which is similar to other international guidelines [53, 65, 66]. However, recently the Swedish Medical Products Agency recommended personalized treatment for individuals with long-term diabetes and with existing complications; the treatment goals could then be less intensive. However, HbA1c > 70 mmol/mol increases the risk of complications and may lead to hyperglycaemic symptoms with impact on the patient's quality of life, and should always be avoided [51, 53]. Despite clear treatment guidelines, good access to healthcare and subsidized GLD, actual achievements of target levels of HbA1c in routine clinical practice are poor. In Sweden less than every second patient with T2DM achieves the recommended HbA1c target levels [67, 68].

3.2 INADEQUATE USE OF MEDICINE

3.2.1 Terminology and definitions

Regular adherence to GLD plays a fundamental role of glycaemic control in improving patients' health outcomes. However, inadequate use of medication is identified as a frequent and age-old problem. The purpose of this section is to provide a short guide regarding the meaning and use of the terms as they relate to evolution of a long-standing problem, Figure 1.

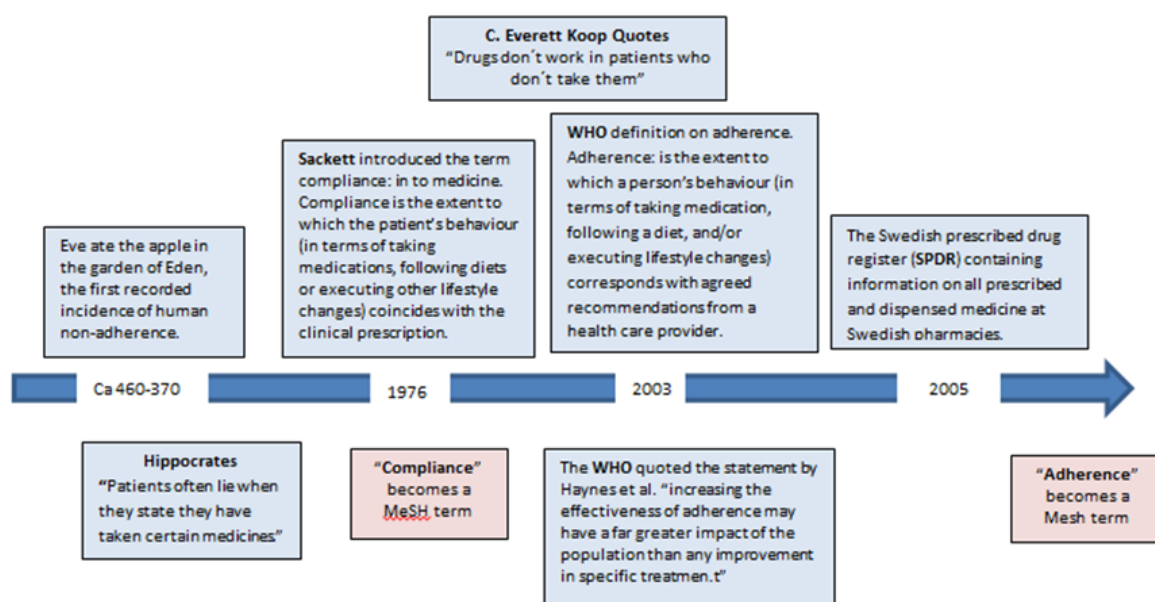


Figure 1. Simplified timeline of terminology for inadequate use of prescribed treatments and quotes adapted and modified from new taxonomy for adherence to medications [69].

There are a variety of terms to describe adherence to medicine and there is a lack of consistency in the terminology. However, compliance, adherence, persistence and concordance are the most widely used terms to describe the adequate use of medicine. The terms are all used when evaluating patients' agreement to prescribed treatment plans, but the terms impose different views and have altered meaning [69-71]. Regardless of the exact term used to describe inadequate use of medicine, the consequences are destructive and with large variation. Some patients will present with therapeutic failure, and others may experience side-effects, some experience disease progression and in the worst cases, premature death. However, this thesis will focus on the term "non-adherence" and the wider expression "inadequate use of medicine", because the latter expression could describe both patients' and providers' erroneous behaviour, including intentional or unintentional inappropriate actions.

Compliance

Compliance is the most common term for describing patients taking their medicine as recommended by their clinician. The expression; "patient non-compliance", was defined in "Compliance in health care" by Haynes et al., 1979 as a lack of coincidence between the patient's behaviour, in terms of taking medications, following diets, or executing lifestyle changes, and clinical prescriptions [10]. Patient compliance has been a Medical Subject Heading (MeSH) term since 1975 [69]. When searching the MeSH term "patient compliance" in the PubMed database it resulted in more than 70,000 publications (Feb. 2019). In literature, compliance refers to a patient who passively follows the physician's orders which indicates that the treatment plan is not a collaboration between the physician and the patient [72].

Adherence

Medication adherence was introduced as a MeSH term in 2009 and represents a more up-to-date term, as it refers to an agreement regarding the treatment plan between the physician and the patient [8, 69]. Adherence is suggested to be separated from the term compliance because of the two-way communication [8, 71]. Today there are more than 15,000 publications with the MeSH term medication adherence. Most of the articles are published later than 2011, in the PubMed database. However, both adherence and compliance refer to the degree to which a patient actually takes the prescribed medicine with respect to timing, dosage and frequency, and many researchers consider the two terms synonymous [71]. Further, compliance and adherence to medicine could both be continuous and categorical variables which could be used to evaluate inadequate use of medicine, over a period of time [71, 73].

Concordance

The term concordance is even more recent but not synonymous with either compliance or adherence. The term was introduced in 1997 and focuses on the healthcare provider and the patient consultation process rather than on a patient's medicine-taking behaviour [70]. It is based on the concept that the consultations between clinicians and patients is a negotiation between equals [74]. The idea is that patients that actively participate in the decision-making will improve medication-taking behaviour [75]. Concordance focuses on the agreement process and does not estimate the patient's behaviour in terms of taking medications.

Persistence

To evaluate how long a patient continues with the treatment, from initiation to discontinuation, compared to the recommended duration is called persistence [69, 71]. Non-persistence is usually evaluated by refill gap algorithms and refers to the absence of dispensed medication within the adequate time period. Non-persistence relates to when a patient decides to stop taking a medicine; the term covers both discontinuers and patients with inadequate use [73]. There are many publications which include the word persistence, but the term is still not a MeSH term. The risk of developing complications is affected by adherence, particularly with regard to how long the patient has been taking the medication. However, a patient who is identified as persistent with the prescribed medicine is not always considered as an adherent patient (Figure 2) [70, 73]. Both adherence and the period of time patients take their

medication affect the medical outcomes, hence both adherence and persistence should be evaluated to characterise adherence comprehensively [71].

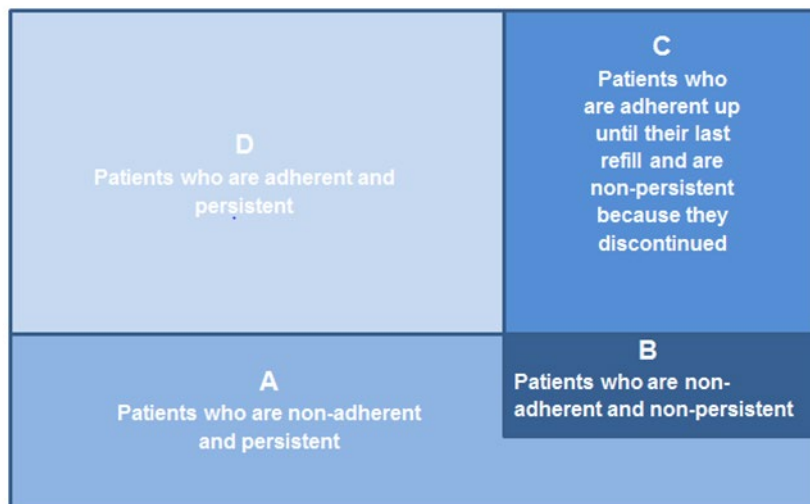


Figure 2. The diagram is illustrating the overlap of non-adherence and non-persistence, adapted and modified from Parker MM et al., *J Am Med Inform Assoc.* 2015 [73]. Non-adherence captures A and B but not C and non-persistence captures B and C.

Prescription drug misuse

“Prescription drug misuse” is a new MeSH term introduced in 2013 describing inadequate use of drugs or medications outside the intended purpose, scope, or guidelines for use. This term differs from medication adherence and is altered from drug abuse, which is more of an obstinate action. Further, prescription drug abuse is a major public health problem [76]. There are already more than 11,000 publications in the PubMed database with the MeSH term “prescription drug misuse”.

Primary non-adherence

Primary non-adherence is when the healthcare provider prescribes a medication, but the medication is never dispensed, meaning that the patient does not initiate treatment at all [77].

Inappropriate prescribing

“Inappropriate prescribing” is a MeSH term introduced in 2011, with more than 2,000 publications in 2019, which describes the practice of administering medications in a manner that poses more risk than benefit, particularly where safer alternatives exist. This term has similarities with the term “prescription drug misuse”, which is defined as improper use of drugs or medicine outside the purpose, scope or guidelines for use.

3.2.2 Measuring adherence

Methods for assessing adherence to medicine

Measurement of medication adherence can be challenging. There are numerous tools available to estimate adherence and a variety of direct and indirect methods to measure this behaviour. However, currently there is no single method to estimate adherence perfectly and a combination of methods is recommended [78-81]. Further, the diversity of methods and absence of a classification of adherence make the interpretation of adherence challenging and limit the ability to compare results from different studies. Approximations of adherence could also differ among diseases or among subgroups of patients, distinguished, for example, in terms of comorbidity, gender, educational level, age, or insurance coverage [82-84]. In this thesis patient-reported outcomes and refill adherence with focus on refill gaps are used to estimate inadequate use of medicine. Most methods for estimating adherence described in the literature are summarised in Table 2.

Table 2. Methods for assessing adherence to medicine [8, 72, 81, 85].

<i>Method</i>	<i>Direct / Indirect</i>	<i>Type of Data</i>	<i>Advantages</i>	<i>Disadvantages</i>
<i>Drug level in biological fluids</i>	Direct	Qualitative	Objective Recent use verified Possible to compare with standardised relationship regarding drug concentration and effect	Data limited to recent use Patient-specific kinetic variations Risk of white coat adherence
<i>Biological markers</i>	Direct	Qualitative	Objective Recent use verified	Data limited to recent use Only yes/no response, no level of adherence Patient-specific kinetic, expensive
<i>Direct patient observations</i>	Direct	Quantitative	Objective Verified use	Impractical in outpatient settings
<i>Patient Interview</i>	Indirect	Qualitative	Easy to use/inexpensive Information about circumstances	Influenced by question construction and interviewer's skill
<i>Patient diary</i>	Indirect	Qualitative	Information about circumstances	Influenced by construction
<i>Patient questionnaire</i>	Indirect	Qualitative	Easy to administer May explain patient behaviour Inexpensive Commonly used method may allow comparisons between studies	Lack of continuous data accuracy is instrument-dependent May overestimate adherence Cognitive or memory limitations may impact assessment
<i>Pill count</i>	Indirect	Quantitative	Objective Easy to use Inexpensive	Lack of medication timing Overestimation of adherence due to "dumping pills"
<i>Pharmacy records</i>	Indirect	Quantitative	Objective Non-invasive Long-term data Large population	Requires comprehensive pharmacy records Dispensed medicine is not equal to ingestion of medicine
<i>Electronic monitoring</i>	Indirect	Quantitative	Continuous data Date and time-specific regarding drug intake	Expensive Inconvenient The patient may open the drug container without taking the correct amount of the drug

Quantification of adherence to medication

Adherence is not always perfect or totally imperfect; it can vary between individuals and may also vary in a given individual over time. However, adherence is often a dichotomized variable, adherent or non-adherent in quantitative evaluations, which is also the case in this thesis. The most common methods for quantifying adherence over a defined time interval are described below [69]:

1. The proportion of drug taken or dispensed
2. The proportion of days with the correct number of doses taken or dispensed
3. The proportion of doses taken, in relation to a defined time interval between consecutive doses
4. The distribution of dose intervals
5. The number of (drug holidays) treatment gaps
6. The longest interval between two doses

Refill adherence

Many researchers have used pharmacy records to estimate refill adherence, i.e. the total amount of dispensed medicine in relation to the number of days between refills [72, 86, 87]. There are several methods to evaluate medication refill adherence, estimate persistence with focus on the duration of drug refill, measure the amount of dispensed medicine in relation to time or assess refill gaps within a period of persistence [88-90].

The Medication Possession Ratio (MPR) method is based on the number (or percentage) of days with dispensed drug during a definite period of time or a period of refill intervals. Another widely used technique is gap measures, e.g. examination of medication gaps (CMG) that estimates if a patient refilled the medication according to the treatment period. These two methods are commonly used to classify patients with good or poor medication refill adherence using “cut-offs” to dichotomize patients [90, 91]. The assumption that could be questioned is that a patient either underuses or stops using the medicine if they do not refill medication as recommended. The most frequent “cut-offs” in the literature for non-adherence is MPR <80% and CMG >30 days [92]. Both MPR and CMG have been found to be appropriate statistics to recognise suboptimal medication refill adherence [29]. However, with a cut-off at 80%, patients are considered as adherent even when they miss one week of medicine during a month. Non-persistence and poor adherence are both associated with extended gaps between refills when using pharmaceutical claims. However, outcomes on refill adherence must be carefully extrapolated, since methods may vary between studies and the choice of method may influence the estimated refill adherence [86, 89, 92, 93]. The major limitation of refill adherence is the estimation of dispensed drugs and not if the patient is really taking the medicine [87]. This is obvious and a well-known dilemma, but dispensed prescriptions are a better surrogate for actual drug intake than a written prescription even if results may overestimate actual adherence.

In this thesis data from pharmacy records are linked with other data stored in population-based registries to explore factors associated with estimated refill non-adherence which is mainly based on medication gaps of glucose-lowering drugs.

3.2.3 Barriers for adherence

Adherence to medication is a complex interaction between the social environment, the patient and the healthcare providers. The problem of poor adherence to medical regimens is commonly recognised and widely researched; however the underlying reasons or contributing factors are still not fully understood. Knowledge of barriers for adherence is a prerequisite for efficient improvement. Non-adherence includes both underuse and overuse even if underuse seems to be more common and therefore more researched. The most common problems associated with taking medicine as prescribed are incorrect doses or delays in the timing of doses [85, 94]. There is a vast heterogeneity in non-adherence which highlights the importance of a broader awareness of the reasons leading to non-adherence or inadequate use of medicine [77].

The patient usually has a reason for missed doses or discontinuation of prescribed medications; many of the reasons are behavioural and non-adherence is therefore often dichotomized by the patients' intent, as non-intentional or intentional [95, 96]. Nevertheless, most patients who are identified to be non-adherent seem to actively choose to neglect the treatment recommendations [96].

Intentional non-adherence

Most people think non-adherence is because of deprived memory or lack of access but it is often an intentional choice by the patient, Figure 3. Intentional non-adherence is associated with an individual's beliefs and cognition. Anxiety of experienced side-effects could cause patients to decrease the dose or stop their refill of medication. A study which included patients from several European countries stated that individuals with T2DM who experienced symptomatic hypoglycaemia reported more obstacles to medication adherence than individuals with no experiences of hypoglycaemia [97].

Insufficient knowledge and negative attitude towards the treatment or an obvious conflict between the treatment recommendation and daily life are considered to be barriers for adherence [96]. Patients are more likely to become non-adherent for chronic diseases where the patient has no or less experiences of unpleasant symptoms [77]. Other barriers associated with intentional non-adherence are feeling well without treatment, lack of motivators or increased personal costs [8, 96, 98]. However, patients usually do not tell a physician (83%) that they are not going to refill the prescription. While the physician believes most patients (91%) adhere to the prescribed regimen, a consequence of the main problem is that non-adherence frequently remains unseen [99].

Non-intentional non-adherence

Non-intentional non-adherence factors are associated with age and clinical variables such as depression, anxiety, and can occur when a patient intends to adhere but is prevented by forgetfulness or incapability, due to different underlying barriers [96], see Figure 3.

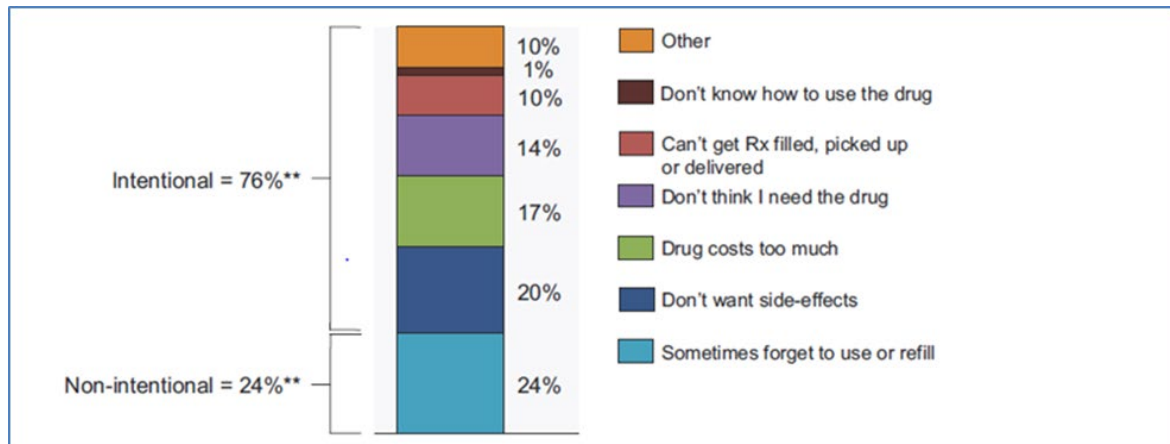


Figure 3. Reasons for non-adherence*.

*Adapted from analysis of a patient survey with 10,000 patients (2002), published in “The hidden epidemic: Finding a cure for unfilled prescriptions and missed doses”, Boston Consulting Group, December 2003, <https://www.bcg.com/documents/file14265.pdf> (attached 2016-06-29) ** Wroe AL (Wroe 2002)

Environmental barriers for adherence

Patient-related barriers represent only a fragment of the variety of problems of non-adherence [8, 100]. Non-adherence is also influenced by complex drug regimens, comorbidity, adverse side-effects, personal costs, unclear agreements between patients and professionals, lack of symptomatology, access barriers, demographic factors and psychosocial issues such as lack of education and socioeconomic-related barriers [8, 72, 77]. Collectively, it has been shown that suboptimal adherence to GLD in individuals diagnosed with diabetes is related to socioeconomic and psychosocial factors [101-104]. Poor health literacy and the talents needed to function successfully in a healthcare environment have been recognised as a possible contributing factor in non-adherence [105, 106].

There is a need for a holistic and better understanding of barriers to improve medication adherence [96, 98]. Furthermore, strategies that address more than one of the barriers simultaneously are recognised as more successful to improve medication adherence and which probably result in improved patient outcomes [98] [107].

3.2.4 Consequences of inadequate use of GLD

Medication non-adherence has several negative consequences for patients, healthcare providers, pharmacies, pharmaceutical companies and society. The consequences of non-adherence to medicine could lead to disease progression, complications, dysfunctional behaviours, poorer quality of life, inflated use of healthcare resources and premature death [77, 108, 109].

Patients with T2DM who dispensed less than 80% of the prescribed GLD over one year were at a significant increased risk of hospitalisation [110]. Moreover, it is shown that high levels of adequate use of medication in individuals with diabetes mellitus were associated with lower disease-related medical costs [111].

The estimated economic burden of inadequate use of medicine makes it a major medical problem globally. Healthcare providers would benefit from follow-up outcomes and consider the possibility of poor adherence to medicine as an explanation for therapy failure. In patients treated with GLD, poor glycaemic control indicates inadequate use of GLD, and occasional non-adherence to medicine which is recognised as one of the primary causes of hyperglycaemic events [68, 69].

It is crucial to study contributing factors related to non-adherence to facilitate the identification of non-adherent patients to be able to design effective interventions for the purpose of improving adherence. Patients, payers, healthcare providers, pharmacies and pharmaceutical companies stand to benefit if patients take their prescribed drugs as directed. Given the complexity in improving medication adherence, achieving mutual benefit most likely requires a collaborative effort from all the parties in the healthcare delivery chain.

3.3 POPULATIONBASED RECORDS

General

This thesis includes data from several established national health registries. Large-scale observational registries are well suited for descriptive studies to investigate associations between patient characteristics and risk of disease and mortality [112]. Sweden has a longstanding tradition of creating nationwide administrative, population-based or disease-specific quality registries, which are a treasure for research. Since 1967, every Swedish citizen and inhabitant has a unique 12-digit personal identification number (PIN) recorded in all registries, which allows person-identification of significant quality and offers an exclusive opportunity to link information from several sources [113]. The data are usually complete and valid, and the coverage is good in the Nordic countries, therefore the limitations are often overlooked. However, the most prominent problems in registry-based research are data selection and data quality, including missing data for some variables [112]. The main strengths of registry-based studies are that data at the time of the study already exist. In addition, study populations are more or less complete; the risk of selection bias is low since data are independently collected. Registry-based studies facilitate research of large populations which enable evaluation of rare conditions and end-points. One of the central limitations includes the probability that important information may be missing or unavailable, data collection is not following a protocol and is not done by the researcher, confounder information is lacking and also information on data quality is missing. Limitations that are inherent to all observational studies must be considered. Because patients are not randomised, it is significantly more difficult to prove a cause-relationship between exposure (e.g. risk factor, treatment) and clinical outcomes of interest.

The national patient registry (NPR)

Information from all 21 county councils in Sweden has been distributed to the National Board of Health and Welfare (NBHW) since 1987 and comprises all in-patient care in Sweden [114]. Since 2001 the registry holds information on all Swedish citizens and residents containing hospital admissions as well as outpatient visits, including day surgery and psychiatric care from all healthcare providers. The coverage of the NPR is nearly 100% [114]. It should be noted that the positive predictive values of diagnoses assigned after hospital admissions due to “trauma and fractures” were found to be 95% or above when compared with medical records [114]. However, there is not yet a national registry covering visits in primary care or outpatient visits to personnel other than physicians (such as nurses, social workers or psychologists) in specialised healthcare facilities. For the individuals included in the studies presented in this thesis, information on discharge diagnosis, using ICD-10 (International classification of disease) and related health problems, has been retrieved [114].

The Swedish prescribed drug registry (SPDR)

The Swedish prescribed drug register (SPDR) is held by the NBHW and contains individual-level data on all dispensed prescription drugs by Swedish pharmacies since July 1, 2005 (100% coverage) [115]. This nationwide registry includes data on dispensed prescriptions of pharmaceutical drugs that individuals have collected from a Swedish pharmacy with the potential of individual-level linkage to other registers. It includes data on prescribed medication, ATC-code, dosage, amounts, and defined daily dose. However, it does not include drugs that are delivered during hospital visits. It is one of the biggest population-based pharma-epidemiological databases in the world and offers high quality data for research [115]. A limitation could be, however, that the SPDR does not include data on over-the-counter drugs.

The Swedish national diabetes registry (NDR)

The Swedish National Diabetes Register (NDR) includes more than 500,000 individuals with diabetes and was initiated by The Swedish Society for Dialectology. The NDR includes more than 92% of individuals who are 18 years of age and diagnosed with diabetes mellitus in Sweden [116]. The registry stores disease-related variables describing patient characteristics.

The longitudinal integration database for health insurance and labour market studies database (LISA)

The longitudinal integration database for health insurance and labour market studies database (LISA) [117] managed by Statistics Sweden provides information about socioeconomic status such as education, income, number of people living in a household and marital status. Since 1990, the database has included complete information on all individuals from 16 years of age. The individual is the main objective, but associations to family, companies and places of employment are also accessible.

National forensic medicine database (NFMD)

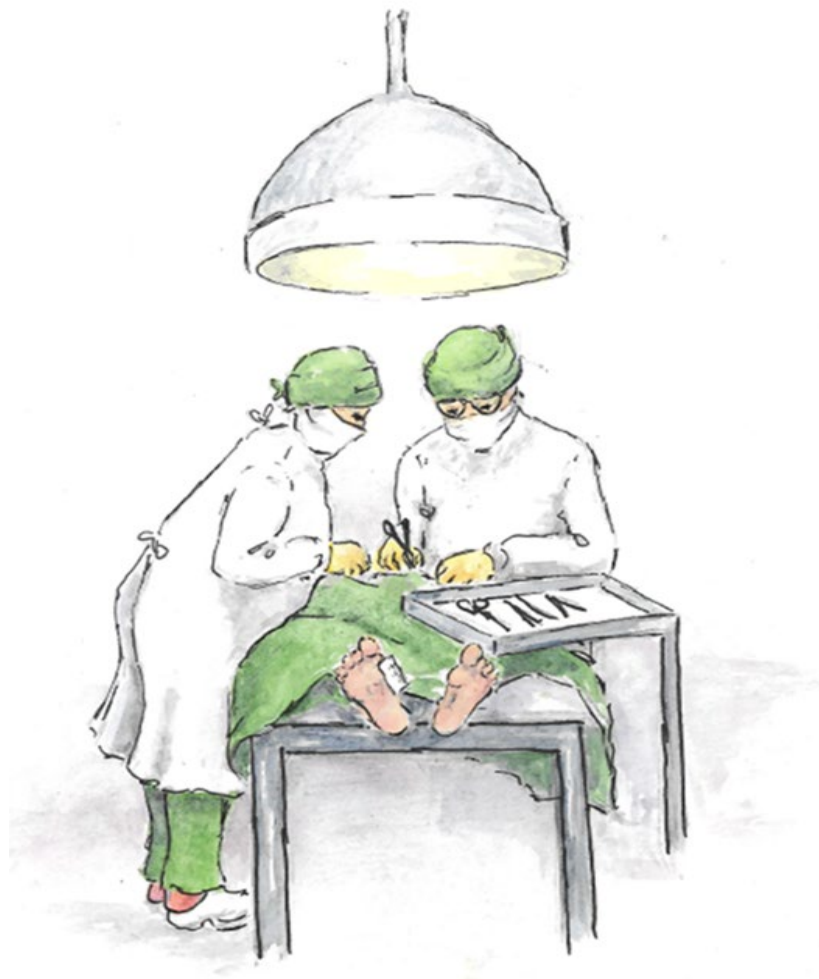
The National Forensic Medicine Database (NFMD) is held by the Swedish National Board of Forensic Medicine and represents a real-time database that is continuously built up of data from the routine casework at this agency. This case management system, originally named RattsBase, was introduced 1991 and in parallel, a similar system was developed for the Swedish national forensic toxicology laboratory. Both systems were developed with the intention to facilitate the routine casework, but also to make it possible to create databases that could cross-talk, in order to allow for evaluation of postmortem toxicological results. The data in NFMD are very reliable since they have been used to generate information on referral notes, labels, autopsy reports that are sent to the police, and death certificates. If errors are noticed in-house or by recipient, the correction will not be in the particular document but in the system, and this correction will automatically appear in NFMD [118].

In Sweden all obvious or suspected unnatural deaths, as well as obscure deaths, should be reported to the police. The police will then almost always decide to request a forensic autopsy. Registered data from postmortem examinations contain detailed information about each subject, including age, sex, cause(s) of death, incidental evidence, and medical history.

In addition, autopsy findings contain outcomes of numerous additional examinations, e.g. microscopy and forensic toxicology, including routinely collected femoral blood, urine and vitreous humour [119].

The Swedish cause of death registry (CDR)

The cause of death registry, now held by The National Swedish Board of Health and Welfare, has been recording mortality with complete information (99.1%) since 1952 [120]. The registry includes data on age, sex, date of death and ICD-10 codes regarding underlying and contributing causes of death [120]. The registry covers mortality data for all individuals who at the time of death were Swedish citizens, regardless of whether the death occurred within or outside the country. In addition, from 2012 it also covers deaths that occurred in Sweden even if the individuals were not Swedish citizens at the time of death [120].



4 STUDIES IN THIS THESIS

Table 3. Studies in this thesis.

	<i>Study I</i>	<i>Study II</i>	<i>Study III</i>
Status	Published	Published	Submitted
Design	Multicentre study, observational	Case control study, observational	Cohort study, observational
Outcomes	Hypoglycaemia Treatment satisfaction Adherence Glycaemic control	Fatal hyperglycaemia Associated risk factors Glycaemic control	Concentration of metformin post-mortem Fatal intoxication Ass. risk factors Glycaemic control
Study sample	Cross-sectional 430 patients in primary care with type 2 diabetes	Retrospective 322 forensic cases with hyperglycaemia + living controls	Retrospective 122 forensic individuals All with metformin in femoral blood
Measure adherence	Indirect measure Patient-reported adherence Dichotomized adherence	Indirect measure Refill adherence; with or without refill gaps	Indirect measure Refill adherence; Daily doses dispensed
Data source	Self-reported questionnaires Medical records	Police reports + NFMD ^a Linked registry data NDR ^b , SPDR ^c , LISA ^d , NPR ^e	Police reports + NFMD Linked registry data NDR, SPDR, NDR NPR
GLD ^f	Metformin/SU	All GLD	Metformin
Type of inadequate use of GLD	Non-adherence, underuse	Non-adherence, underuse, inadequate use	Non-adherence, overuse, inadequate use, inappropriate prescription
Statistics	Tests; Student's t, Kruskal-Wallis, Mann-Whitney U, χ^2 Cochran Mantel –Haenszel	Tests; Student's t, χ^2 Mann-Whitney U test Odds ratio Univariate logistic regression	Tests; Student's t, χ^2 Mann-Whitney U test Kruskal-Wallis
Consequences of inadequate use of GLD	Analysis of covariance Test of independence Adverse events, hypoglycaemia Glycaemic control	Multiple logistic regression Death due to hyperglycaemia Glycaemic control	Death due to metformin intoxication Glycaemic control
Studied risk factors	Symptomatic hypoglycaemia Treatment satisfaction Barriers for adherence	Comorbidity Diabetes-related variables Socioeconomic status Psychosocial status Pathology	Comorbidity Diabetes-related variables Psychosocial status Pathology

a) National forensic medicine database

b) The Swedish national diabetes registry

c) The Swedish prescribed drug registry

d) The longitudinal integration database for health insurance and labour market studies database

e) The national patient registry

f) Glucose lowering drugs

5 AIMS

General Aim

The overall aim of this thesis is to examine consequences derived from inadequate use of GLD in individuals with diabetes mellitus in Sweden as well as to further explore risk factors for serious consequences of inadequate use of GLD.

Specific Objectives:

- I.** To study the impact of symptomatic hypoglycaemia on medication adherence, and on patient satisfaction with treatment, in relation to glycaemic control in patients with T2DM treated with a combination of metformin and sulfonylurea.
- II.** To identify potential risk factors associated with confirmed fatal hyperglycaemia in individuals on glucose-lowering drugs.
- III.** To determine fatal and non-fatal postmortem femoral blood reference concentrations of metformin, and to explore possible risk factors for fatal metformin intoxication.

6 STUDY POPULATIONS

General: The overall aim of this thesis is to examine inadequate use of GLD in individuals with diabetes mellitus in Sweden. Accordingly, we have studied three different Swedish populations with assumed diabetes, with observable consequences that might indicate inadequate use of GLD.

Study I: At 54 primary care accounts, 430 consecutive patients with T2DM, 35 years of age or older, treated with metformin and SU dual therapy were recruited by Swedish investigators between January 2009 and August 2009. Patients were enrolled during a regular visit at their general practitioner from all 21 county councils in Sweden. The centres represent a homogeneous cross-section of the Swedish diabetes population since the centres were of diverse sizes and located in different demographic areas, both rural and urban.

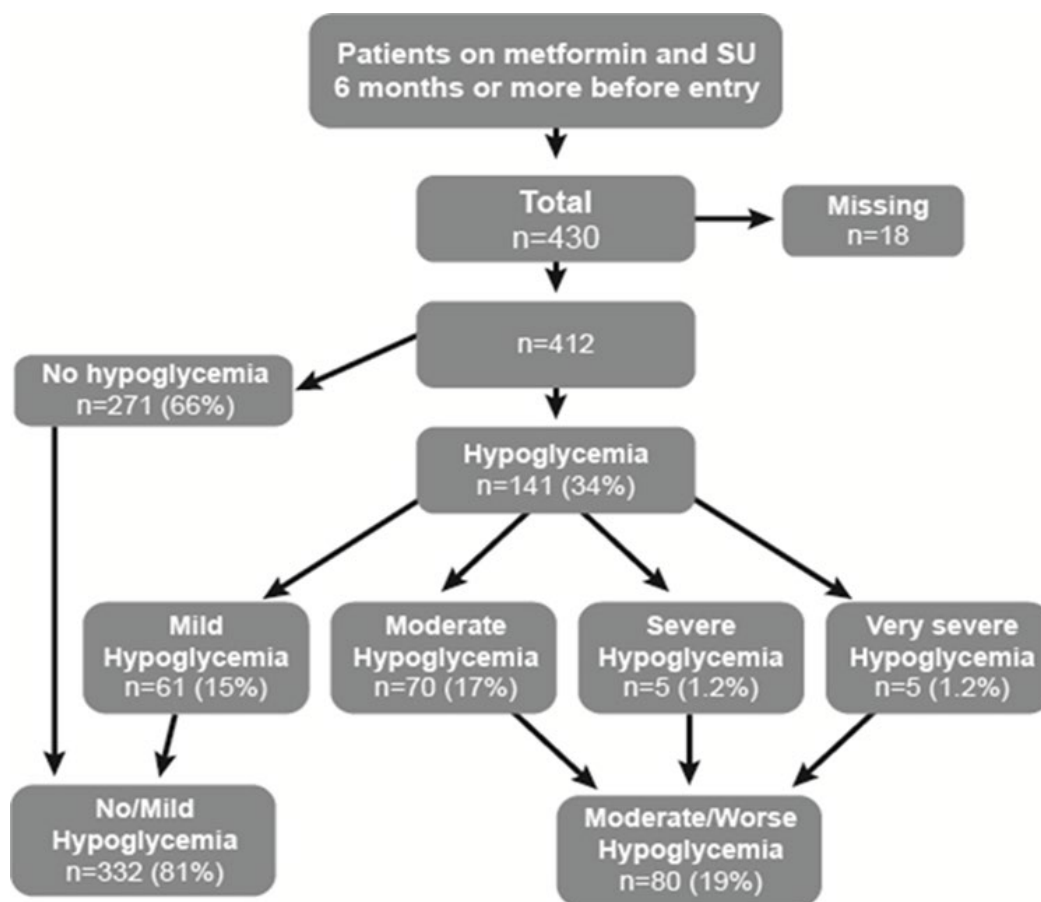


Figure 4. Selection of study population in Study I.

Study II: Once the study cohort had been defined, in the NFMD comprising 322 individuals who died due to confirmed hyperglycaemia in Sweden from August 2006 to December 2012, registry data from four additional sources were obtained via linkage to the personal identification numbers of included patients. Deceased subjects (268) with recognised dispensed GLD were matched on age and sex, with living controls randomly selected in the SPDR. Each control was given an index date equal to the date of death of the matched case.

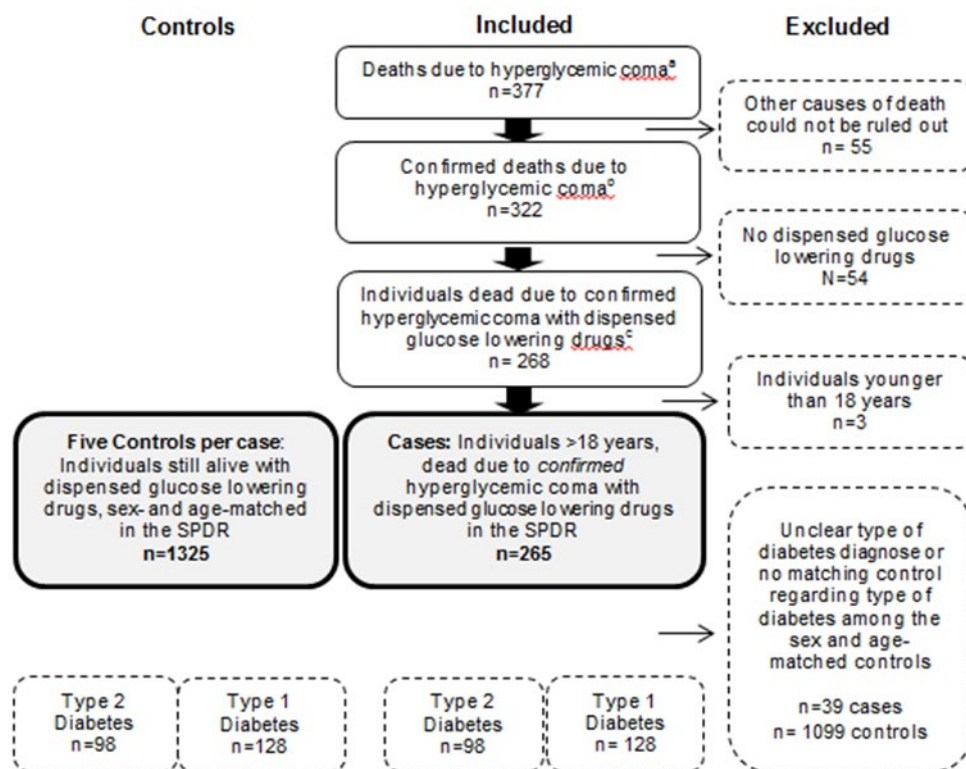


Figure 5 Selection of cases and controls included in the study population in Study II.

- a) Identified in the national forensic medicine database (NFMD) in Sweden August 2006 to December 2012
- b) Death due to hyperglycaemic coma confirmed by two independent forensic pathologists
- c) Data retrieved from the Swedish prescribed drug registry (SPDR)

Study III: This study population comprises all individuals with metformin in postmortem femoral blood, from September 2011 to December 2016 in Sweden. It was a retrospective registry-based cohort study, conducted on a nationwide group of 122 deaths where metformin was identified in forensic autopsies and registered in the NFMD. All included patients had dispensed metformin at a Swedish pharmacy the year before death and every patient with a recorded diabetes diagnosis in the NDR or NPR were diagnosed with T2DM.

7 METHODS

In this thesis, a variety of indirect methods has been used to evaluate inadequate use of medication, since there is no gold standard to determine inadequate use [78-81]. Further, a diversity of consequences related to inadequate use of GLD have been scrutinised as well as pre-defined associated risk factors in the included papers in this thesis.

7.1 SELF-REPORTED QUESTIONNAIRES

In Study I, a number of self-reported questionnaires were used to evaluate experiences of symptomatic hypoglycaemia, treatment satisfaction and adherence to medicine.

Hypoglycaemia

The Worry subscale of HFS-II estimated worry and anxiety around hypoglycaemic experiences, with a subscale of 18 items, and a 5-point Likert scale ranging from 0 (never) to 5 (very often) were used [121-123]. Moreover, scores were compiled from a validated questionnaire covering 10 items on the frequency and seriousness stratified patients by severity of symptoms (none, mild, moderate, severe or very severe), consequently with earlier study dichotomized into no or mild symptoms and moderate or worse symptoms [122]. In line with a published review, the patients' experiences of the interruption of ongoing activities in everyday life, due to the severity of symptoms of hypoglycaemia, was the platform for stratification [124].

Treatment Satisfaction Questionnaire for Medication

The TSQM (version 1.4), a validated questionnaire, estimated patient satisfaction with treatment which covered four elements: Side-effects (four items), Effectiveness (three items), Convenience (three items) and Global satisfaction (three items). A score per element was considered ranging from 0 to 100, a higher score indicating superior satisfaction with treatment.

Self-reported adherence and barriers

Self-report is the most common method for assessing adherence in research and clinical care. Patients reported adherence to treatment in a questionnaire covering 13 items where response was indicated by yes/no or by using a 5-point Likert scale (five items) or an 8-point Likert scale (three items). Because of the potential risk of overestimating adherence, it is recommended to stratify adherence as a dichotomous variable when using self-report [125, 126]. Therefore every patient who reported any failures following agreed treatment instructions regarding the GLD were categorised as non-adherent, which is in line with other studies that have used the same survey [97, 127, 128].

7.2 FORENSIC MEDICINE AND TOXICOLOGY DATA

Forensic toxicology provides the basis for Study II and III in the present thesis, and therefore warrants some attention. Toxicological detection of pharmacological substances is central to modern forensic investigation, since a substantial proportion of the people in the western world regularly uses pharmaceutical drugs, and since the analysis for drugs is critical for the diagnosis of fatal intoxications and/or for the assessment of degree of influence of drugs in other forms of unnatural deaths. Femoral blood, urine and vitreous fluid, when available, are consistently collected at almost every forensic autopsy in Sweden. In most cases, alcohols and certain other small volatiles, such as acetone are analysed with head-space gas chromatography. Since September 2011, the femoral blood samples are subjected to a liquid chromatography (LC-MS-TOF) screening that covers almost all regularly encountered drugs on the market as well as most illegal drugs [129]. Before that a gas chromatographic screening with nitrogen-phosphorous detector (GC-NP) was used for screening of drugs [130]. Positive findings are confirmed with a variety of quantitative LC-MS or GC-MS methods. Certain drugs with complex chemical structures and properties, e.g. anabolic androgenic steroids, may not be captured by the screening, and will be analysed with special methods upon request. All the analyses are performed at one central laboratory, the National forensic toxicology laboratory at the Swedish National Board of Forensic Medicine. This laboratory has since several decades participated in analytical exchange programs and performed well compared to other forensic toxicology laboratories. The responsible forensic pathologist will interpret the results, often after discussion with the toxicologists. Reference information on postmortem blood drug levels are extensively used, in particular the reference data that has been generated from the NFMD data according to a strategy previously described [130].

In Study II and III nationwide cohorts of deceased were selected from all the forensic medicine departments in Sweden. In Sweden, all obvious or suspected unnatural, unexpected or obscure deaths should be reported to the police. The police will then request a forensic autopsy in most of these cases. Information from the police and other sources, the forensic pathology and the forensic toxicology results are registered in a case management system, and a similar system is used at the national forensic toxicology laboratory [118]. These systems represent real-time databases, combined into the National Forensic Medicine Database (NFM D), hence extensive and detailed data are available for all fatal intoxications examined [118].

The study populations in Study II and III were identified by a search profile that takes advantage of a very precise cause of death registration. The PIN of the subjects together with a selection of variables containing relevant information for each study was submitted to the NBHW. Before that, the relevant information from the autopsy reports, police reports and medical records, when available, was transformed into computable variable in the file submitted. The NBHW then linked these data with selected information from population based registries and replaced the PIN with a serial number to ensure anonymity. Hence the final file from the NBHW contained both the forensic medicine and toxicology information,

and the information from the national registries held by NBHW, including comprehensive information about the history of comorbidity, dispensed pharmaceuticals, and socioeconomics and diabetes health-related variables from linked registries. The nationwide cohorts in this thesis have an advantage over most other similar epidemiological studies since the characteristics of the study populations and circumstances surrounding death are very well documented.

Confirmed death due to hyperglycaemia

Diabetes mellitus has become a major cause of death and hyperglycaemic episodes occur frequently in acute illness in individuals with or without diabetes. In Study II the focus was on acute hyperglycaemic episodes that could have caused or contributed to death rather than identifying patients with the disease. Independent forensic pathologists scrutinised autopsy results, police reports and other relevant information with the aim of finding confirmed deaths due to hyperglycaemia. In clinical practice, the most important biochemical markers to identify disorders in glucose metabolism are blood glucose concentration and glycated haemoglobin levels. However, postmortem it is difficult to identify disorders in glucose metabolism as a cause of death due to major changes in body fluids and other tissues [122, 123]. The HbA1c is stable for several weeks after death, but short episodes of hyperglycaemia do not affect HbA1c, and hence HbA1c cannot be used to disclose an acute fatal hyperglycaemia [123, 124]. Further, the blood glucose concentration is not reliable postmortem since the blood glucose concentrations rapidly decrease to zero after death due to the extensive consumption by the surviving blood cells [131].



However, vitreous humour is better preserved than blood after death, and a suitable matrix for analysis of glucose and other endogenous compounds. The vitreous body is a colourless, transparent gel that fills up the eyeball, and is devoid of cells. The eyeball has an isolated position, which makes it protected from postmortem changes and less affected by contamination and degeneration after death [132]. After an initial decrease in vitreous glucose levels during the first 24 hours, the glucose concentration in the vitreous stays stable [133]. Further, Zilg et al. reported that glucose levels >10 mmol/l in vitreous fluid strongly indicates fatal hyperglycaemia [133]. Accordingly, the primary inclusion criterion for fatal hyperglycaemia in Study II was a vitreous glucose level of > 10 mmol/L and where other causes of death could be ruled out. As a matter of fact, vitreous glucose values of 10 mmol/L are equivalent to about 26 mmol/L in blood [134]. Accordingly, patients in Study II most likely had glucose levels of at least 26 mmol/L (and in the majority of cases much higher levels) in blood before their demise [133].

Deaths with detection of metformin

Screening for drugs has been routinely used at forensic toxicology laboratories for decades. In 2011, a new liquid chromatography/time-of-flight mass spectrometry (LC-MS-TOF) screening for drugs was introduced at the Swedish national toxicological laboratory [129]. This method can detect metformin, but like all other substances no quantitative results can be provided. Instead there is a LC/MS/MS verification method for metformin that can be used, either if the peak area of metformin is very large, or if the responsible forensic pathologist specifically requests an analysis of metformin.

The initial population consisted of individuals where metformin was detected in femoral blood postmortem and logged in the NFMD. Two independent reviewers evaluated autopsy results, police reports and, when available, medical charts to stratify the cases as postmortem control cases or intoxication cases. A case was only included in the study if consensus between the two reviewers had been reached. However, forensic toxicology can only provide an estimate of substances present in a body at the time of sampling; hence, information of substances taken or exact doses of the consumed substances can often not be obtained [135].

The control group in Study II, henceforth group C, consisted of postmortem cases where metformin was detected but the cause of death clearly excluded the incapacitation by this drug or other substances. Intoxication was ruled out in C cases since they were capable of an active action, according to a previously described procedure [130]. First, a rough selection was made based on the primary cause of death diagnosis by the forensic pathologist, and then all cases were subjected to a manual assessment by two independent reviewers. A case was only classified as a control case when consensus between the two reviewers had been reached. This strict inclusion and exclusion criteria as well as a manual multi-reviewer, case-by-case evaluation for determination of fatal and non-fatal concentrations of pharmaceutical drugs has been applied for more than two decades [130, 136-138]. The postmortem control

group (C) is mainly comprised of violent suicides and selected accidental trauma deaths, where incapacitation by drugs can be ruled out.

Refill adherence

In Study II and III pharmacy records are used for assessing refill adherence with the purpose of reflecting the continuity of medication use and capturing the timeliness and frequency of refill. Refill gap measures were used to identify patients who show inadequate medication refill adherence using “cut-offs” to dichotomize patients as being adherent or non-adherent [90, 91]. Many studies of medication non-adherence and non-persistence have used refill gaps algorithms, but the predefined allowable gap varies from 7-180 days. However, the most frequent cut-off in the literature to detect non-adherences is a predefined gap of 30 days or more [92]. In Sweden, one drug prescription typically corresponds to a maximum of three months’ continuous treatment, based on the structure of the Swedish reimbursement system [67, 86]. Therefore, patients with a minimum gap of 125 days between two dispenses of GLD were classified as inadequate refill adherence to medication [67, 139]. This method may be used regardless of product and dosage of the regimen. Hence, individuals with no evidence of dispensed GLD drugs 125 days or more before death/index date were considered as non-adherent/non-persistent.

Matched case-control design

In Study II, a matched case-control design was used. Matched studies are common in the scientific literature, and their benefits and shortcomings have been extensively discussed [140]. It has been suggested that the main advantage of a matched case-control study is its ability to adjust for confounding [141], as well as a better effectiveness compared to an unmatched study [142]. However, by matching on a variable assumed to be a confounder, there is the possibility that a selection bias has been introduced, since the exposure among controls does not represent the exposure in the source population [141, 142]. Regarding study II, we matched deceased with living subjects treated with GLD regarding age and gender in our effort to control for confounders, but we cannot eliminate that we may have introduced a selection bias.

Possible risk factors

Several recent systematic reviews highlight a variety of factors that may be associated with non-adherence in patients treated with GLD, but further research is warranted to identify modifiable factors, since knowledge of risk factors is critical for improvement of adherence [13, 143, 144]. In this thesis, we studied selected factors that we considered relevant in clinical practice and which could be associated with inadequate use of GLD.

In Study I, experiences of hypoglycaemia and treatment satisfaction were evaluated. Methods are described earlier in this thesis (self-reported questionnaires).

In Study II and III, comorbidity as well as disease-related factors were scrutinised as potential significant real-world risk factors. Relevant information was retrieved from the NDR and NPR; ICD-10 codes in the NPR were used to identify potential risk factors before the date of death/index. Examples of examined factors: history of macrovascular events, microvascular complications, last recorded HbA1c value, BMI, fatty liver disease, and history of psychiatric illness, including depression. Further, substance abuse was studied in both Study II and III. Individuals were categorised with substance abuse problems if they had a recorded discharge diagnoses of ICD-10 codes F10-19 (representing substance abuse, plus possible substance of abuse intoxication) [145] and/or if there was evidence of hospitalisation or outpatient hospital consultation at a clinic for substance abuse, retrieved from the NPR. In addition, we used police reports to identify well-known substance abuse.

In Study II we also examined information about socioeconomic factors, including education level, income level, number of inhabitants in a household, employment status and marital status, collected from the LISA registry. In Study III we had no data from the LISA and therefore used information from the police reports to identify individuals living in a single household.

7.3 STATISTICS

Data were analysed using different versions of Microsoft® Office Excel 2010 software and SPSS v. 25, for Windows (SPSS Inc., Chicago, IL, USA). All tests were two-tailed and conducted at a significant level of $p < 0.05$.

Descriptive statistics and hypothesis testing:

Characteristics of individuals are presented as mean (\pm SD) with 95% CI for normally distributed variables (tested with Kolmogorov-Smirnov test); otherwise median and percentiles (25th-75th perc) are presented. Categorical variables are presented as number and proportions (%).

Dissimilarities between groups are estimated using Student's t-test or Mann Whitney U test for continuous variables and Chi-square tests for categorical variables, as appropriate. Further, the Kruskal-Wallis test was used when more than two groups were compared as in Study III when the medians of metformin were evaluated. All group comparisons in Study I were adjusted for differences in age, and p-values were assessed by means of analysis of covariance for continuous data and the Cochran Mantel-Haenszel test for categorical data. In Study I, the dependence between adherence and experiences of hypoglycaemia was tested. The test of independence was used to study the association between variables in cross tables; the null hypothesis was classified as the independent, meaning that Pearson Chi-squared P-values < 0.05 indicated a dependence between variables.

In Study II logistic regression analysis was used to obtain the odds ratio for predefined explanatory variables for fatal hyperglycaemia (the dependent variable). To categorise variables associated with confirmed fatal hyperglycaemia, variables probably associated with death due to hyperglycaemia were dichotomized and the odds ratios were at a first step calculated using univariate logistic regression models. Variables showing an association with fatal hyperglycaemia ($p < 0.05$) were included into multiple logistic regression analyses using a stepwise elimination backward technique, where the least significant variable was removed for each step. We used the stepwise elimination backward technique to improve the prediction power with a minimum number of variables. The results were expressed as odds ratios (OR) with 95% confidence interval (CI).

8 RESULTS

8.1 GENERAL

This thesis demonstrates several serious consequences that may derive from inadequate use of GLD, including that 20% of the patients treated with metformin and SU experienced serious hypoglycaemia, more than 300 individuals treated with GLD died outside hospitals due to confirmed hyperglycaemia during the study period in Study II. In addition 17 individuals died during 2011-2016 due to unintentional metformin intoxication in Sweden.

Inadequate use of GLD is an ongoing important problem with multifaceted expression, including refill gaps of GLD, self-reported non-adherence and inappropriate prescribed GLD. This thesis also reveals several risk factors associated with inadequate use of GLD.

Noteworthy, a significant number of individuals identified with fatal hyperglycaemia were most likely undiagnosed, fatal hyperglycaemia was the first manifestation of diabetes mellitus.

Finally, the results from all studies collectively showed an overall poor achievement of HbA1c target based on the treatment goals stated in the Swedish national guidelines.

8.2 RESULTS FROM SPECIFIC STUDIES

8.2.1 Study I

In this study we found that almost one in three patients treated with metformin and SU experience any form of hypoglycaemia. More importantly, one in five patients experienced hypoglycaemic episodes of such severity that their daily activities were interrupted.

The main finding is that adherence is negatively associated with the severity of the experienced hypoglycaemic symptoms (Figure 6A).

Patients with moderate or worse symptoms of hypoglycaemia reported poorer adherence to medication (46% versus 67%, $p < 0.001$) than patients with no or mild symptoms (Table 4).

The patients with moderate or worse symptoms of hypoglycaemia had significantly lower mean HbA1c values than patients with no or mild symptoms (7.0% versus 7.3%, $p < 0.05$) even though a greater proportion of patients with no or mild symptoms reported that they were adherent to GLD.

Further, this study verifies that only 40% of the patients treated with metformin and SU in a primary care setting achieved the HbA1c target based on the treatment goals stated in the Swedish national guidelines.

Table 4. Patient characteristics and study groups of no/mild symptoms versus moderate/worse symptoms of hypoglycaemia and groups of adherent versus non-adherent patients. Data expressed as the mean standard deviation for continuous variables and as a percentage for categorical variables.

	Total (n=430)	No/mild (n=332)	Moderate/worse (n=80)	P-value	Adherent (n=260)	Nonadherent (n=143)	P-value
Age (years)	69.0 (9.5)	69.8 (9.1)	64.6 (9.9)	0.001*	70.3 (9.5)	66.3 (8.9)	0.001*
BMI (kg/m ²)	28.7 (4.3)	28.8 (4.4)	28.5 (4.1)	0.23	28.8 (4.4)	28.6 (4.3)	0.30
HbA _{1c} (mmol/L) latest value [†]	7.2 (1.0)	7.3 (0.8)	7.0 (0.8)	0.03*	7.2 (1.0)	7.2 (1.1)	0.62
Fasting blood glucose (mmol/L)	8.4 (2.2)	8.5 (2.3)	7.9 (2.0)	0.08	8.3 (2.0)	8.5 (2.4)	0.35
Total cholesterol (mmol/L)	4.6 (0.9)	4.6 (0.9)	4.5 (0.9)	0.47	4.5 (0.9)	4.6 (0.9)	0.27
Cholesterol LDL (mmol/L)	2.6 (0.8)	2.6 (0.8)	2.6 (0.7)	0.64	2.6 (0.8)	2.6 (0.8)	0.61
Triglycerides (mmol/L)	1.8 (0.8)	1.8 (0.9)	1.7 (0.8)	0.21	1.7 (0.8)	1.8 (0.9)	0.33
Cholesterol HDL (mmol/L)	1.2 (0.4)	1.2 (0.4)	1.2 (0.3)	0.53	1.2 (0.4)	1.2 (0.4)	0.87
Systolic BP (mmHg)	137.1 (15.8)	137.8 (16.3)	134.4 (14.6)	0.30	137.9 (15.8)	135.4 (16.0)	0.37
Diastolic BP (mmHg)	76.3 (9.1)	76.6 (8.9)	75.5 (9.7)	0.04	76.6 (9.3)	75.8 (8.7)	0.06
Tablets/day (n)	4.8 (1.4)	4.7 (1.4)	4.8 (1.5)	0.75	4.8 (1.4)	4.7 (1.3)	0.55
Gender: male	60.7	60.2	62.5	0.85	56.2	69.3	0.07
Diabetes duration >7 years	71.0	70.8	70.9	0.51	71.9	70.0	0.83
History of microvascular event	18.8	19.9	14.5	0.50	17.9	21.5	0.28
History of macrovascular event	32.6	32.4	33.3	0.32	36.5	27.1	0.50
Goal attained (HbA _{1c}) [‡]	40.4	38.6	48.1	0.14	38.2	42.0	0.49
Married	12.4	13.3	8.9	0.23	12.4	11.8	0.63
Higher education	14.3	12.5	21.5	0.12	12.9	17.2	0.49
Physical activity	75.9	74.9	80.0	0.53	77.7	71.7	0.16
Smoking	12.1	12.3	11.2	0.64	10.0	15.0	0.47
No change in treatment	85.2	84.9	86.2	0.86	87.3	81.7	0.15
Adherent	67.0	67.1	46.2	0.01*			
Nonadherent	37.0	32.9	53.8	0.01*			
Moderate/worse hypoglycemia					14.5	28.7	0.003*

[†] 7.0% DCCT-standard (52 mmol/mol), [‡] HbA1c goal according to Swedish national guidelines. Missing patients are excluded, p-values age adjusted, * $p < 0.05$

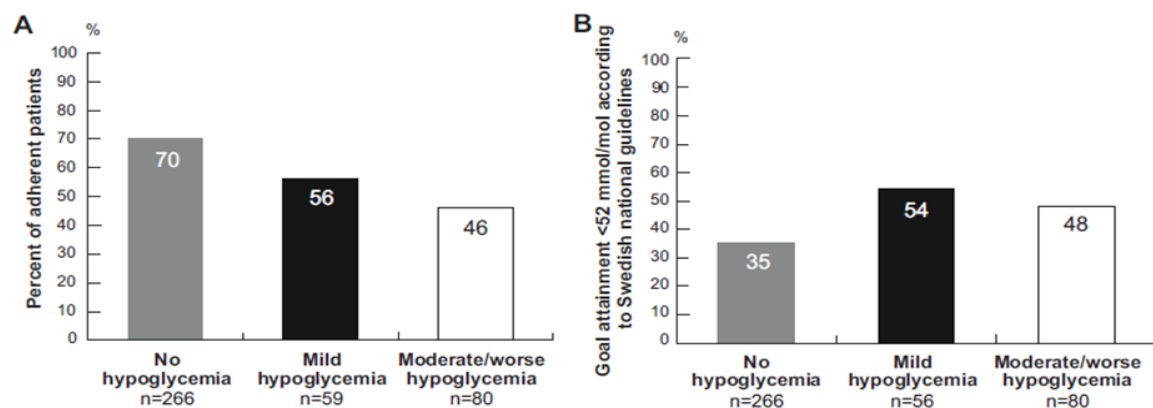


Figure 6. (A) Proportion of patients who reported adherence with glucose lowering drugs in relation to severity of symptoms of hypoglycaemia. (B) Proportion of patients with HbA1c goal achievement based on the national guidelines in relation to severity of hypoglycaemic symptoms.

Test of independence, Pearson's chi-squared test, $p < 0.005$. Missing patients were excluded.

Patient reported outcomes measures (PROM) indicated that a number of predefined barriers to adherence were more frequent in patients with moderate or worse hypoglycaemia compared to patients with no or mild symptoms, shown in Figure 3.

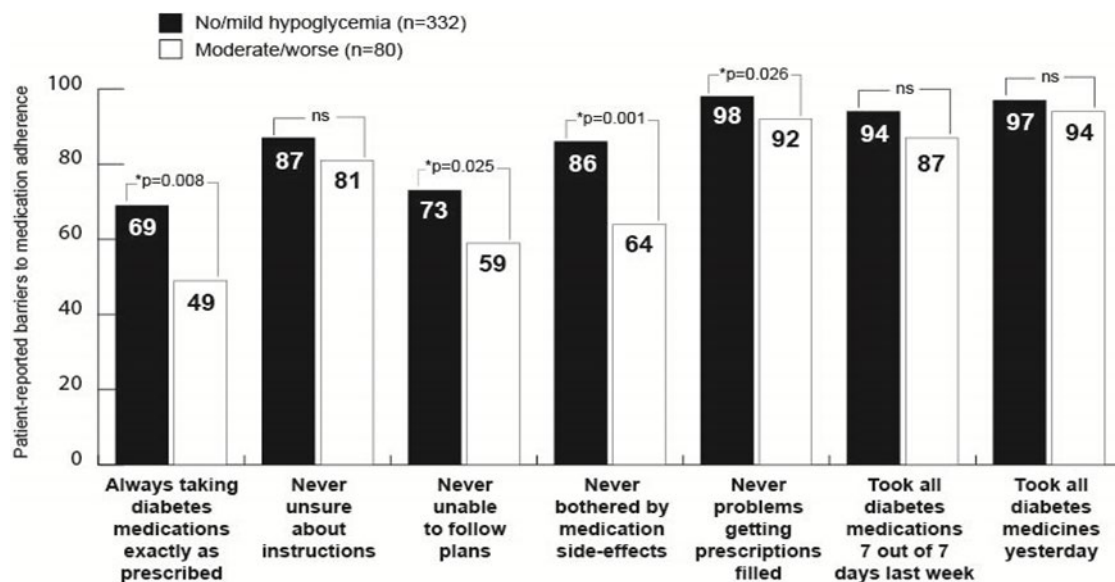


Figure 7. The overall scores of reported adherence and barriers to adherence (%) in the no/mild symptoms and moderate/worse symptoms of hypoglycaemia study groups age adjusted p-values.

Patients with no or mild symptoms of hypoglycaemia were more satisfied with the actual glucose-lowering treatment than the patients with moderate or worse symptoms (Table 5).

Table 5. Treatment Satisfaction Questionnaire for Medication (TSQM) scores for all patients as well as the categories no/mild and moderate/worse hypoglycaemia. Data expressed as means and standard deviation (SD).

	All patients (n=430)	No/Mild (n=332)	Moderate/Worse (n=80)	p-value
TSQM dimension: Effectiveness (0-100)	69.7 ± 10.9	70.3 ± 10.8	67.7 ± 11.2	0.029*
TSQM dimension: Side effects (0-100)	92.9 ± 16.2	94.4 ± 14.0	87.1 ± 21.8	0.0001*
TSQM dimension: Convenience (0-100)	75.1 ± 12.0	75.6 ± 12.1	73.9 ± 11.6	0.081
TSQM dimension: Global satisfaction (0-100)	70.3 ± 16.1	71.2 ± 16.2	67.0 ± 16.0	0.036*

Notes: P-values are age adjusted missing patients are excluded data are expressed as the mean and standard deviation *p<0.05. Abbreviations: TSQM, treatment Satisfaction Questionnaire for Medication

8.2.2 Study II

In this study the 322 included deceased individuals with fatal hyperglycaemia had a mean concentration of vitreous glucose of 39.5 ± 19.4 mmol/L, which indicates very high blood glucose levels (≥ 75 mmol/L) antemortem [133].

The majority of the deceased with confirmed fatal hyperglycaemia were males (79%); most of them (71%) were between 45 and 75 years of age and treated with GLD (83%) and the majority had a history of insulin treatment. The police reports indicated that most of the cases who died due to fatal hyperglycaemia were dying alone (76%) and almost half of the cases (47%) had no diabetic medicine at the scene. Further, the overall glycaemic control was very poor. In diseased subjects 47% had an HbA1c ≥ 75 mmol/mol at the last healthcare visit. A significant number of the deceased (n=48, 15%) in this study had no dispensed GLD and no identifiable records of diabetes in the NPR.



Risk factors associated with fatal hyperglycaemia

This study evaluated several predefined risk factors that may have contributed to fatal hyperglycaemia. In summary, we found that several risk factors were significantly associated with increased risk of fatal hyperglycaemia. Table 6 shows odds ratios and CIs for all the risk factors associated with fatal hyperglycaemia.

Table 6. Results of the multiple logistic regression analyses, odds ratios and 95% confidence intervals for risk factors of fatal hyperglycaemia in individuals treated with GLD.

Variables (yes/no) no = reference n= 265 cases/controls with diabetes	OR	95% CI	p
Type 1 diabetes ^a	1.93	1.13-3.30	0.017
Insulin treatment	4.40	1.96-9.85	<0.001
No refill of GLD before death ^b	3.87	1.99-7.53	<0.001
HbA1c \geq 75 mmol/mol	2.00	1.23-3.27	0.005
Microvascular disease	3.26	1.84-5.79	<0.001
Psychiatric illness	2.30	1.32-4.01	0.003
Mental disease due to substance abuse	23.8	4.57-123.6	<0.001
Substance abuse	8.85	2.34-35.1	0.002
Current smoker	1.81	1.06-3.09	0.029
Single household	2.25	1.21-4.18	0.010
Married ^c	0.39	0.17-0.87	0.022

Variables that showed significance ($p < 0.05$) in the univariate analysis were included in the multivariate analysis. Backward stepwise conditional logistic regression model was applied in 7 steps in all subjects.

a. Diagnosed with type 1 diabetes, type 2 as reference

b. Patients with no dispensed GLD drugs 125 days or more before death/index

c. Married or registered partnership versus reference: unmarried, divorced, widow or widower

8.2.3 Study III

Between September 2011 and December 2016, 120 patients with metformin detected and quantified in postmortem femoral blood were included in the study. The majority of the population were middle-aged men. The metformin intoxication was considered to be intentional only in five (23%) of the single drug intoxications (A) and in three (23%) of the multiple drug intoxications (B). The intoxications had significantly higher median concentrations of metformin in femoral blood versus controls but had not dispensed higher mean doses/day of metformin than controls. In this study the glycaemic control is poor with only 37% reaching the HbA1c target. Participants' characteristics for cases and controls are presented in Table 7A and 7B.

Table 7A. Characteristics of all individuals with confirmed metformin in femoral blood based on autopsy results, police reports and population-based registries. All subjects were stratified as single substance intoxication (A), multiple intoxication (B), postmortem controls (C) and cases with another cause of death (O). Number of individuals (%), mean (\pm SD) or median (25th-75th perc).

Variables	A	B	C	O
<i>Number of cases</i>	22 (100%)	7 (100%)	13 (100%)	78 (100%)
<i>Metformin median (μg/g)</i>	48.5 (30.5-98.0)	21.0 (8.20-26.0)	2.3 (1.25-5.35)	4.6 (1.78-8.78)
<i>Metformin (μg/g)min-max</i>	13.0-210	4.40-95.0	0.70-21.0	0.64-54.0
<i>Gender (male)</i>	14 (63.6%)	5 (71.4%)	10 (76.9%)	58 (74.4%)
<i>In the NDR ^a</i>	20 (90.9%)	5 (71.4%)	12 (92.3%)	70 (89.7%)
<i>Type 2 diabetes ^b</i>	21 (95.4%)	6 (85.7%)	13 (100%)	71 (91.0%)
<i>Insulin ^c</i>	12 (54.5%)	2 (28.6%)	5 (30.8%)	29 (37.2%)
<i>Sulphonylureas ^c</i>	8 (36.4%)	2 (28.6%)	7 (53.8%)	24 (30.8%)
<i>Living alone</i>	19 (86.4%)	7 (100%)	9 (69.2%)	56 (71.8%)
<i>Suicide</i>	5 (22.7%)	3 (42.8%)	4 (30.8%)	4 (5.1%)
<i>Known alcohol abuse</i>	17 (77.3%)	5 (71.4%)	5 (38.5%)	32 (41.0%)
<i>Ongoing infection</i>	6 (27.7%)	0 (0%)	0 (0%)	15 (19.2%)
<i>Dehydration</i>	6 (31.6%)	1 (14.3%)	0 (0%)	15 (19.2%)
<i>History of CKD</i>	9 (40.9%)	2 (28.6%)	3 (23.1%)	18 (23.1%)
<i>History of heart failure</i>	1 (4.5%)	0	0	7 (9.0%)
<i>History of stroke</i>	4 (18.2%)	1 (14.3%)	0 (0%)	4 (5.19%)
<i>History of CVD</i>	11 (50.0%)	1 (14.3%)	0 (0%)	18 (23.1%)
<i>Any contraindications ^d</i>	20 (90.9%)	6 (85.7%)	7 (53.8%)	51 (65.4%)
<i>Drugs with interactions ^e</i>	15 (68.2%)	4 (57.1%)	9 (69.2%)	62 (79.5%)
<i>Age (years)</i>	66.4 (\pm 10.2)	61.0 (\pm 12.1)	65.9 (\pm 10.9)	66.4 (\pm 9.7)
<i>Age min-max</i>	37-80	37-77	43-80	41-90
<i>BMI kg/m² ^f</i>	26.8 (\pm 5.60)	29.6 (\pm 5.38)	31.6 (\pm 8.8)	28.9 (\pm 6.9)
<i>eGFR ml/min/1.73 m² ^f</i>	80.2 (\pm 26.3)	69.1 (\pm 15.3)	71.9 (\pm 15.3)	75.2 (\pm 17.0)
<i>eGFR <60 ml/min/1.73 m²</i>	6 (27.3%)	2 (28.6%)	3 (23.1%)	12 (15.4%)
<i>HbA1c (mmol/mol) ^f</i>	52.6 (\pm 12.7)	49.6 (\pm 14.4)	57.3 (\pm 11.8)	62.1 (\pm 21.6)
<i>Diabetes duration</i>	11.5 (\pm 7.7)	10.5 (\pm 3.5)	12.1 (\pm 5.6)	12.5 (\pm 8.7)
<i>Metformin (g/day) ^g</i>	1.50 (0.75-2.25)	1.50 (0.25-6.37)	1.50 (0.85-2.00)	1.25 (0.62-2.50)
<i>Higher dose than SPC ^h</i>	4 (18.2%)	3 (49.3%)	4 (30.8%)	21 (26.9%)

- a) Registered in the NDR
- b) Diagnosed with T2DM versus no confirmed diabetes diagnosis
- c) With dispensed drug from pharmacies during the same period as dispensed metformin
- d) With any contraindications to the use of metformin according to the SPC
- e) With dispensed drugs with risk of interactions with metformin according to SPC
- f) At last healthcare visit, registered in the NDR
- g) Estimated mean dispensed dose of metformin from pharmacies (g/day) last 90 days
- h) Estimated mean dose metformin higher than recommended daily dose in SPC, adjusted for kidney function

Table 7B. Characteristics of individuals with metformin in femoral blood classified as intoxications (single substance intoxication (A) + multiple intoxication (B)) or controls (controls (C) + cases with another cause of death (O)). All significance tests are two-tailed. Number of individuals (%), mean (\pm SD) or median (25th-75th perc).

Variables	Intoxications (A+B)	Controls (C+O)	p-value
<i>Number of cases</i>	29	91	
<i>Metformin median (μg/g)</i>	41.0 (22.5-68.0)	4.10 (1.70-8.40)	0.001*
<i>Age (years)</i>	65.1 (\pm 10.73)	66.2 (\pm 9.82)	0.88
<i>Gender (male)</i>	19 (65.5%)	68 (74.7%)	0.348
<i>In the NDR ^a</i>	25 (86.2%)	82 (90.1%)	0.732
<i>Insulin ^c</i>	14 (48.3%)	34 (37.5)	0.384
<i>Sulphonylurea ^c</i>	10 (34.5%)	31 (34.1%)	1.00
<i>Living alone</i>	26 (89.8%)	65 (71.4%)	0.050 *
<i>Known alcohol abuse</i>	22 (75.9%)	37 (40.8%)	0.001*
<i>Ongoing infection</i>	6 (20.7%)	15 (16.5%)	0.780
<i>Dehydration</i>	7 (26.9%)	15 (16.5%)	0.259
<i>History of CKD</i>	11 (37.9%)	21 (23.1%)	0.148
<i>History of heart failure</i>	1 (3.45%)	7 (7.69%)	0.678
<i>History of stroke</i>	5 (17.2%)	4 (4.4%)	0.037*
<i>History of CVD</i>	12 (41.4%)	18 (19.8%)	0.027 *
<i>Any contraindication ^d</i>	26 (89.7%)	58 (63.7%)	0.010 *
<i>Drugs with interactions ^e</i>	19 (65.5%)	71 (78.0%)	0.219
<i>BMI (kg/m^2) ^f</i>	27.4 (\pm 5.59)	29.3 (\pm 7.26)	0.307
<i>eGFR (ml/min) ^f</i>	78.0 (\pm 24.67)	74.7 (\pm 16.7)	0.892
<i>eGFR < 60 (ml/min)</i>	9 (31.0%)	15 (16.5%)	0.111
<i>HbA1c (mmol/mol) ^f</i>	52.0 (\pm 12.8)	61.4 (\pm 20.5)	0.018 *
<i>HbA1c < 52 (mmol/mol)</i>	16 (64.0%)	28 (34.1%)	0.011 *
<i>Diabetes duration (years)</i>	11.3 (\pm 7.09)	12.4 (\pm 8.31)	0.812
<i>Dispensed metformin (g/day) ^g</i>	1.50 (0.75-3.50)	1.25 (0.75-2.50)	0.663
<i>Higher dose than SPC ^h</i>	7 (24.1%)	25 (27.5%)	0.813

- a) Registered in the NDR
- b) Diagnosed with T2DM versus no confirmed diabetes diagnosis
- c) With dispensed drug from pharmacies during the same period as dispensed metformin
- d) With any contraindications to the use of metformin according to the SPC
- e) With dispensed drugs with risk of interactions with metformin according to SPC
- f) At last healthcare visit, registered in the NDR
- g) Estimated mean dispensed dose of metformin from pharmacies (g/day) last 90 days
- h) Estimated mean dose metformin higher than recommended daily dose in SPC, adjusted for kidney function

Reference concentrations

The result shown in Figure 8 demonstrates that the median concentration of metformin in single intoxications, group A (48.5 µg/g, range 13.0-210 µg/g) and in multiple intoxications, group B (21.0 µg/g, range 4.40-95.0 µg/g) were both significantly ($p<0.05$) higher compared to the median concentration of metformin in controls, group C (2.30 µg/g; range 0.70-21.0 µg/g). The median blood concentration of metformin in intoxications (A+B) was ten times higher than the concentrations in controls (C+O). There was no statistical difference between the median concentration of metformin in group C compared with the median in group O (4.60 µg/g, range 0.64-54.0 µg/g).

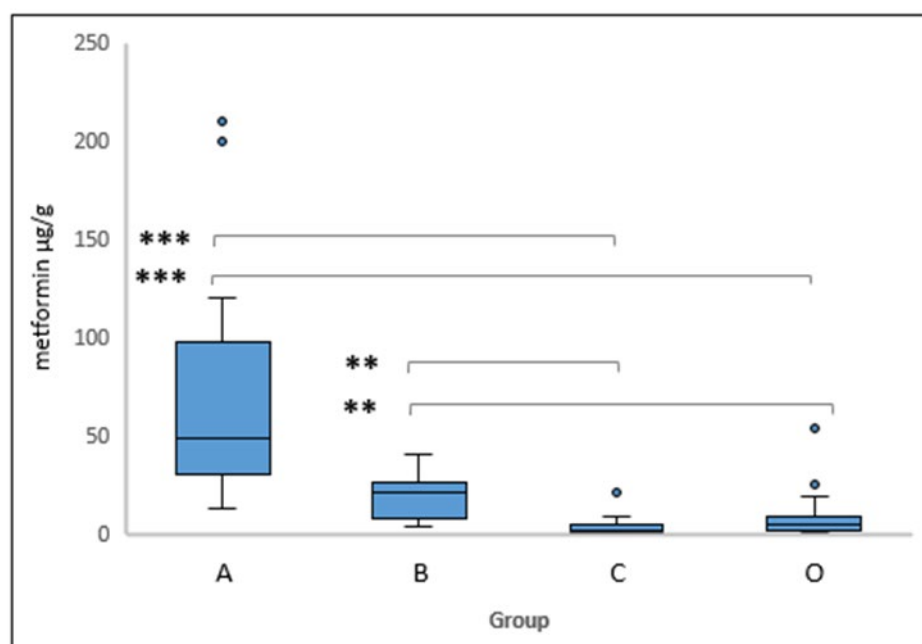


Figure 8. Median post-mortem concentrations (µg/g) of metformin in femoral blood.

Kruskal-Wallis test, independent samples, pairwise comparison, * $p<0.05$, ** $p<0.01$, *** $p<0.001$

Risk factors for metformin intoxication

A greater proportion of intoxications (A+B) than controls (C+O) had one or more of the contraindications for the use of metformin (89.7% ($n=26$) versus 63.7% ($n=58$, $p<0.05$). In addition, alcohol abuse was a prominent contraindication that was in itself significantly associated with fatal intoxication. Other important possible risk factors regarding fatal metformin intoxication included living alone, history of cardiovascular disease, stroke and/or an HbA1c (<52 mmol/mol). The values for each valued risk factor are presented in Table 7B. The median dispensed daily dose of metformin over the last 90 days or the last year did not differ between intoxications and controls. Further, several of the deceased had dispensed drugs, other than metformin, which indicated increased risk for interactions with metformin, but there were no statistical differences between groups. The discrepancies in proportions (%) of risk factors between intoxications and controls are presented in Figure 9.

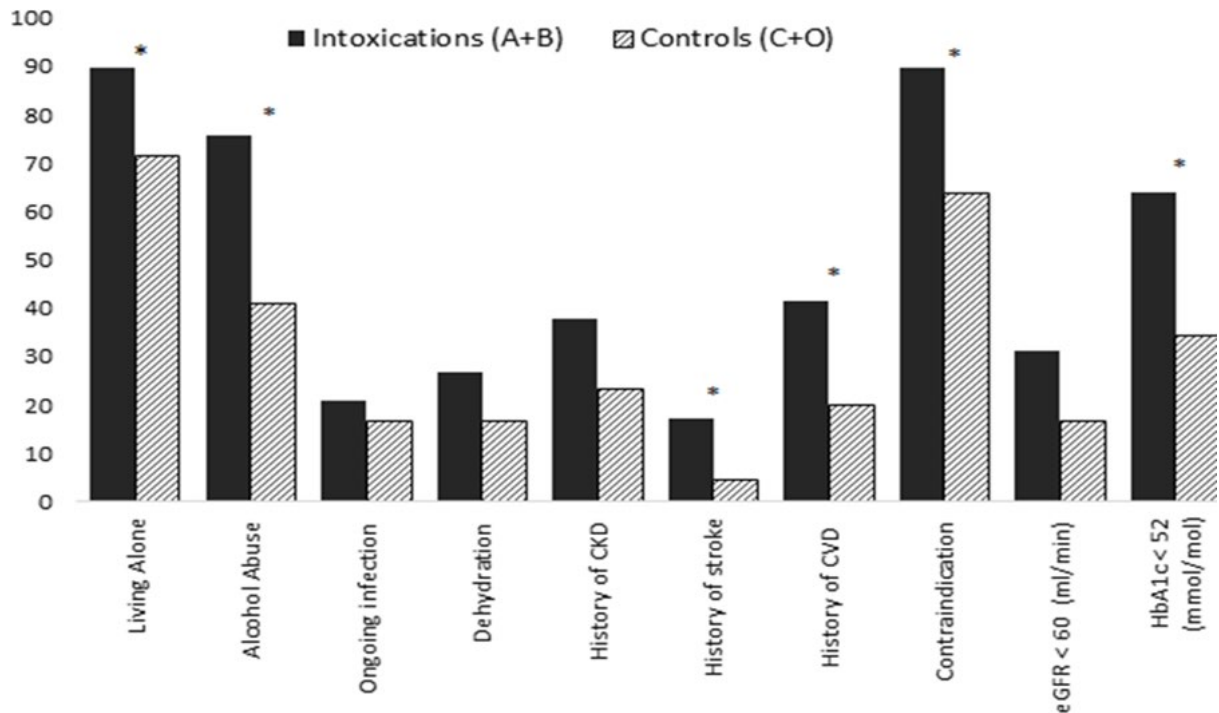


Figure 9. Risk factor characteristics, presented as (proportion, %) for intoxications (A+B) versus controls (C+O), and group differences evaluated by appropriate test statistics. All tests were two-tailed. Number expressed as %, *= $p < 0.05$.

Abbreviations: cardiovascular arterial disease (CAD) cardiovascular disease (CVD), chronic kidney disease (CKD), arterial fibrillation (AF)

9 DISCUSSION

General

This doctoral thesis aims to evaluate consequences of inadequate use of GLD in individuals with diabetes mellitus and to contribute to a better awareness of risk factors associated with these consequences.

First, this thesis shows several serious **consequences associated with inadequate use of GLD** in a Swedish diabetes population. This thesis suggests that experiences of hypoglycaemia, fatal hyperglycaemia and fatal intoxication of metformin are indications of consequences of inadequate use of GLD in clinical practice.

Second, this thesis illustrates different aspects of **inadequate use of GLD**. We found a significant number of individuals with confirmed refill gaps, self-reported non-adherence, non-persistence with medicine, and clinical inertia, including prescribing a GLD to patients with contraindications to the use of the drug.

Third, this thesis presents several identifiable **risk factors associated with inadequate use of GLD**, which is important since non-adherence to medicine is often unknown and the most critical first step in improving adherence is recognition of its absence. This thesis highlights risk factors associated with inadequate use of GLD such as, for example, poor glycaemic control, psychosocial factors, alcohol abuse, experiences of side-effects and living alone, which may lead to serious consequences for patients due to inadequate use of GLD.

There has been extensive research on non-adherence over the past decades. The present thesis confirms the recent review that states that non-adherence to GLD remains an essential ongoing problem that still needs attention [13]. Similar to the aim of this thesis, the review highlights the need for awareness of identifiable and modifiable risk factors associated with non-adherence to improve management of T2DM [13].

This thesis addresses the problems associated with inadequate use of GLD. An appropriate use of pharmaceutical drugs is a key factor to the success of a patient's treatment.

Consequences associated with inadequate use of GLD

Poor glycaemic control

The main finding was that all the studies in this thesis collectively confirm a wide discrepancy between recommended HbA1c targets and actual achievements, since almost half of the study population in every study had uncontrolled diabetes [67, 68]. The population in Study I managed by the primary care centres had good access to healthcare and a variety of subsidized GLD but despite this, only 40% of the patients achieved the HbA1c target as defined by the national treatment goals [53].

In Study II, 47% of the deceased showed elevated HbA1c levels (≥ 75 mmol/mol) at the last healthcare visit, which doubled the risk for fatal hyperglycaemia. Interestingly, the results showed that microvascular disease was also a significant risk factor associated with fatal hyperglycaemia which suggests that the deceased most likely had a history of poor glycaemic control since microvascular complications are related to long-lasting poor glycaemic control [146]. Our findings show a strong association between poor glycaemic control and fatal hyperglycaemia in agreement with recent findings that show that a history of poor glycaemic control is associated with an increased risk of all-cause mortality in patients with diabetes [49]. Further, the results confirm that individuals who died due to hyperglycaemia more often showed an inadequate refill adherence of GLD, probably the cause for developing hyperglycaemia that caused or contributed to death.

Hypoglycaemia

The main finding was that patients with moderate or worse symptoms of hypoglycaemia reported poorer adherence to medication than patients with no or mild symptoms. Hypoglycaemia has been suggested to be one of the main limiting factors for achieving adequate glycaemic control due to the association with poor adherence because of the side-

effects, particularly among patients treated with SUs [147-149]. Self-reports in Study I demonstrated that experiences of hypoglycaemia have a negative impact on both adherence to medication and patient satisfaction with treatment. This thesis emphasises the importance of a wider understanding of patient-reported experiences and preferences in order to improve the management of diabetes mellitus.

In Study I, one out of five patients was experiencing hypoglycaemic episodes of such severity (moderate or worse symptoms) that their daily activities were in some way interrupted due to disturbing and worrying symptoms. The proportion of patients who reported any experience of hypoglycaemia (34%) was similar to the proportion previously reported in studies of patients treated with SUs [147, 148]. However, since there is no consensus on the definition of hypoglycaemia in the literature, it is difficult to compare studies on hypoglycaemia. Our classification of hypoglycaemic episodes is consistent with the definition used in widely recognized reviews on the subject [124, 150]. The finding that patients in Study I who were experiencing moderate or worse episodes of hypoglycaemia actually had lower HbA1c than those who reported no or mild hypoglycaemia is expected, since hypoglycaemia can be considered as a consequence of low HbA1c [151]. But still important because, symptomatic hypoglycaemia could need more clinical attention since it is associated with poorer adherence to GLD, shorter persistence to GLD and lower quality of life, which may have a negative impact on health outcomes in patients with T2DM [6, 79, 122, 152-155].

The results of Study I suggest that glycaemic control is achieved at the expense of symptoms of hypoglycaemia in patients treated with metformin and SU. The T2DM patients walk a fine line between glycaemic control and symptoms of hyperglycaemia and worries about hypoglycaemia and the consequences seem to refrain both patients and physicians from following appropriate treatment recommendations [151, 156-159]. Study I highlight the importance of PROM to identify symptoms of hypoglycaemia and dissatisfaction with treatment to personalize the treatment regimens to improve management of type 2 diabetes.

Fatal Hyperglycaemia

The main discovery in Study II was that individuals with fatal hyperglycaemia were more likely to have poor refill adherence of GLD versus living controls, which probably was the reason for developing a fatal hyperglycaemia. Actually, 26% of the cases had not refilled any GLD over the 3 months prior to death. The results were confirmed by police who reported that there was no GLD found at the scene in almost half of the cases (47%).

During the study period we identified 322 cases with fatal hyperglycaemia with elevated vitreous glucose levels with a mean concentration of 39.5 ± 19.4 mmol/L. The results indicate life-threatening levels of blood glucose at the time of death since a vitreous glucose level of 10 mmol/L is equivalent to about 26 mmol/L in blood, and the majority of cases had far higher levels [134, 160].

We believe that fatal hyperglycaemia is overlooked if vitreous glucose is only analysed upon suspicion, and suggest that this analysis should be performed in all autopsy cases [73, 161]. The observations in Study II as well as those reported by Zilg et al [133] are important for practitioners to be aware of.

Metformin intoxication

The main finding was that metformin in most cases was prescribed to patients despite contraindications, warnings or precautions to metformin use, including renal dysfunction and alcohol abuse. The prevalence of alcohol and medication interactions is widespread but could need some more attention in clinical praxis to improve the appropriate use of medicine [162, 163]. Further, fatal and non-fatal concentrations of metformin in postmortem femoral blood were established. The median concentration of metformin in postmortem femoral blood in intoxications was significantly higher than the median level of metformin in controls. However, the metformin concentration varied from 13-210 µg/g in single intoxications. The result confirms previous case reports and postmortem studies with a similar range of metformin concentration in individuals who died due to metformin poisoning [164, 165].

The comprehensive information from police reports and the NFMD was enriched with robust information regarding the history of comorbidity, dispensed pharmaceuticals and diabetes health-related variables from the linked registries. The fatal and non-fatal reference concentrations reported in Study III will hopefully be helpful in cases where for evaluation of cases where the circumstances surrounding death are unclear. Given that the study cohort is very well characterised and fairly large, it seems reasonable to suggest intoxication with metformin as a cause of death when the postmortem femoral blood level exceeds 10 µg/mL.

Undiagnosed diabetes

We found 48 (15%) individuals with confirmed fatal hyperglycaemia, who were undiagnosed and had no evidence of dispensed GLD. Most of these individuals (85%) were older than 45 years of age and most likely individuals with undiagnosed T2DM. The result confirms previous estimates that many individuals with T2DM are probably undiagnosed and suggests that Sweden may have a noteworthy number of adults with unknown T2DM, and that death in diabetic coma could be the first manifestation of diabetes [20, 166]. The presented risk factors may be helpful for health care providers to decide to perform physical examinations, including blood glucose analysis, to identify individuals with undiagnosed diabetes.

Inadequate use of GLD

Non-adherence

The main outcome in Study I was the significantly negative association with adherence and severity of the experienced hypoglycaemic symptoms. Further, patients with moderate or worse symptoms of hypoglycaemia reported poorer adherence to medication, more barriers to adherence to medicine and also reduced treatment satisfaction than patients with no or mild symptoms. This thesis suggests that healthcare providers should consider PROM to identify non-adherence and improve the management of diabetes mellitus in clinical practice.

Study I showed that the mean HbA1c was lower in the group of patients with worse symptoms versus the group with no or mild symptoms even if they reported better adherence. However, with the variety of methods and lack of definition of adherence, results should be compared with some caution. Notably, others have demonstrated that the relationship with non-adherence and uncontrolled diabetes occurs more frequently in studies measuring adherence via refill adherence than self-report measures [161, 167, 168]. A possible weakness with Study I may be that self-reports tend to overestimate adherence. To minimise the risk of overestimation we dichotomized adherence and turned the focus onto detecting non-adherence, since self-reports of non-adherence usually are reliable, “a patient who admits to poor adherence is generally being candid” [72]. However, the proportion of non-adherent patients may have been underestimated, even if self-report adherence measures most likely provide good specificity and weak sensitivity for detecting poor adherence [126, 169].

The main finding in Study II was that a larger proportion of individuals who died due to hyperglycaemia had inadequate refill adherence of GLD compared to living controls, which confirms that non-adherence is most likely one of the primary reasons for hyperglycaemic events. Moreover, since non-adherence is a common problem among a general population with diabetes mellitus, it is reasonable to believe that the magnitude of non-adherence to medicine or inadequate use of GLD may be even higher among patients with identified poor glycaemic control [170]. Therefore, this study suggests a need for clinical attention to poor glycaemic control and improved skills to evaluate adherence as well as appropriateness of treatment in the clinical setting.

Clinical inertia

In Study I the result showed no differences in glycaemic control when comparing the adherent group with the non-adherent group which made us aware that adherence to medication only makes sense if a suitable dose of an effective and safe regimen of GLD is prescribed [171, 172].

Accordingly, this thesis suggests a wider approach to non-adherence and a preference for the wording “inadequate use” since both a patient’s behaviour and a physician’s clinical inertia represent key obstacles to adequate use of GLD. Optimal adherence is crucial for the success of a patient’s treatment and most studies show that adherence to GLD is associated with

better glycaemic control in clinical practice [7, 139]. The result in Study I was unexpected but even more important since it showed that we should not put all the focus or responsibility on the patient to adhere to medicine without evidence that an appropriate medicine with an adequate dose was prescribed. It has been reported that clinical inertia, including inadequate prescribing, seems to be even more common than non-adherence to GLD in patients with poorly controlled diabetes [173]. In line with this, others have claimed that non-adherence contributes to poor glycaemic control in patients with diabetes mellitus in Sweden, but this is probably not the only reason since about 90% had satisfactory refill adherence in a general population with T2DM treated with oral GLD [174].

Alternatively, therapeutic decisions could be based on unreliable assumptions of adherence, which may lead to an increase of doses or adding another GLD due to poor glycaemic control, which may lead to severe consequences.

Poor glycaemic control in patients treated with GLD should lead to a comprehensive review of the situation to find the most reasonable explanation, including non-adherence, poor efficacy of medicine, inadequate doses, interactions, contraindications or other prescription error, to improve HbA1c target achievement and patient satisfaction.

Study III shows that the metformin intoxication was confirmed to be intentional only in eight cases (23%). Therefore, it is crucial to remember in the postmortem context that high drug concentrations may not always be due to an acute high intake but could result from accumulation of metformin due to impaired elimination. Ultimately, we should not exclusively focus on the patient's responsibility to minimise the risk of stigmatisation of intoxicated patients.

It is well known that treatment with metformin is considered to be contraindicated in individuals with acute or chronic conditions that may cause lactic acidosis such as renal dysfunction, infections, dehydration, trauma, heart failure, myocardial infarction, liver insufficiency, advanced age or alcohol abuse [13, 39]. However, in Study III the most common precipitating factor in single intoxications was any contraindication (90.9%) quantified as: chronic or acute alcohol abuse (77.3%), renal dysfunction (40.9%), severe ongoing infection (27.7%) or dehydration (31.6%). In addition, 68% of intoxications were simultaneously treated with prescribed pharmaceuticals with increased risk of interactions with metformin.

However, metformin is extensively used since the drug offers effective glycaemic control and additional effects that contributes to significant clinical improvement. A large Swedish study showed that individuals with T2DM treated with metformin were at lower risk of death than those with insulin or other oral treatments [175]. Further, the study showed that metformin lowered the risk of severe outcomes also in individuals with T2DM and renal dysfunction [175]. The results of the latter study have contributed to the recent revision of the metformin treatment in patients with renal dysfunction. The benefits of metformin seem to outweigh most of the risks of the treatment. However, from what we know there is little information

regarding treatment with metformin in patients with other contraindications and warnings to the use of metformin than renal dysfunction. The high proportion of subjects with alcohol abuse observed in these studies warrants attention, even if the cohort is biased by the select cases that are subjected to a forensic autopsy.

Risk factors associated with inadequate use of GLD

This thesis has identified several contributing risk factors associated with consequences of inadequate use of GLD.

First, Study I demonstrates that experiences of side-effects such as hypoglycaemia could be considered as a risk factor since such experiences may have a negative influence on adherence to medications and a negative impact on patient satisfaction with treatment. Hypoglycaemia may not only be a risk factor, but also be a consequence of inadequate use of GLD.

Second, Study II showed that the risk of death due to fatal hyperglycaemia was higher among individuals treated with insulin compared to those treated with oral anti-diabetic drugs. In addition, Study II showed that poor glycaemic control and elevated HbA1c values were strong risk factors for fatal hyperglycaemia, an acute event caused by uncontrolled diabetes. In most cases, the reason for developing fatal hyperglycaemia was probably the poor refill adherence of GLD.

In addition, Study II confirms an association between non-adherence and psychosocial factors, previously reported [101-104, 161, 176, 177]. The risk of fatal hyperglycaemia was significantly increased in patients living in a single household, and/or who had a history of psychiatric illness or with evidence of substance abuse. For this reason, the understanding of a patient's psychosocial status in clinical practice may be equally important as other more traditional and well-known risk factors when improving the management of T2DM patients.

Third, Study III shows a high correlation between fatal metformin intoxication and alcohol abuse (75.9%). This is an interesting observation since older adults frequently use pharmaceuticals that may interact with alcohol and lead to undesired effects [40]. It has been reported that alcohol abuse and its effects seem to be associated with hypoglycaemia and/or lactic acidosis in diabetic patients treated with metformin [40, 41]. The results suggest that clinicians should consider monitoring the alcohol consumption and inform patients who are prescribed alcohol-interactive drugs about the risk of undesired effects to minimise the risk of metformin intoxications. Hence, healthcare providers should be aware of the potentially serious effects of metformin when prescribed to patients with alcohol abuse or other contraindications. However, our results should be interpreted with caution considering the select population and the possible presence of confounders among these subjects [178, 179].

Finally, poor glycaemic control was frequently observed in all three studies and has been recognized as a common consequence of non-adherence or inadequate use of GLD. Uncontrolled diabetes in general could be considered a key risk factor; it is easy to identify

and is significantly associated with non-adherence and other forms of inadequate use of GLD [7, 180-182].

Strengths and limitations

A general limitation applicable for all the studies is that we have no information about to what extent the patients actually used their medication, since it cannot be proven that the patients took the medication after it was dispensed from the pharmacy. Further, we have no information on how the physicians in fact prescribed the medicine; we could only evaluate dispense patterns.

A major strength of data collected from registries as a source of data for research is that they mirror clinical practice and are free from the recall bias that may be seen in data collected through patient surveys. One of the strengths of the two studies based on the NFMD is that the study populations are very well characterised because of the linkage with other registries.

To link registries could boost results when data from independent sources confirm each other's findings. From the NFMD we collected information that showed that the police found no GLD medicine at the death scene in most (>50%) of the cases. This information confirms the data retrieved from the SPDR that a large proportion of individuals who died due to fatal hyperglycaemia had no or very poor refill adherence of GLD.

However, the fact that data collected from registries reflect clinical practice may also be a potential weakness. Since data are not recorded for research purposes or according to a strict protocol, values for variables such as HbA1c are only available whenever these tests were conducted in clinical practice and not at systematic intervals as in clinical trials.

As mentioned before, it is difficult to estimate the actual intake of medicine. There was no evidence that intoxications had dispensed more than maximal daily doses of metformin from pharmacies, but that does not exclude an acute high intake.

The routines for analysis of vitreous glucose and metformin upon suspicion of diabetic coma and metformin intoxication, respectively, imply that it is likely that some cases may go undetected. This selection bias in Study II and III to include cases with specific case circumstances probably means that the numbers of diabetic coma and metformin intoxications are underestimated. Another overall limitation may be that the cohorts that underwent forensic autopsy may not be entirely representative of all individuals at risk of metformin intoxications or fatal hyperglycaemia which may limit extrapolation of our results.

10 ETHICS

General

The aim of the thesis was to contribute to a deeper understanding of inadequate use of GLD and identify risk factors. However, we need to do this with caution, since some of the pre-defined variables, e.g. substance abuse, mental disorder or living alone could be associated with indignity. More importantly, in order to minimise the risk of stigmatisation of patients with chronic diseases, we should not put all the responsibility on the patient to succeed with treatment.

Study I included patients who were recruited by approved investigators between January 2009 and August 2009. After having given consent to participate in the study, patients filled out questionnaires. Data on patient characteristics and medical record data were logged into an online form by healthcare providers. Investigators also completed a web-based case report form on laboratory values, medical history and GLD. The patients in the study did not undergo any intervention since they were treated according to clinical practice. Therefore, we expected no increased risks or extraordinary benefit for patients participating in the study. A database was formed for compiling questionnaire and patient records data using anonymous patient numbers. Patients' questionnaire data were entered into the database and analysed at group levels. The study protocol was approved by the Regional Ethics Review Board in Linköping (Dnr M185-08).

In **Study II and III** the forensic pathology findings and forensic toxicology results in the NFMD were retrieved for each cohort. The unique PIN was used to link data in the NFMD with population-based Swedish databases. Typically the ethical review boards in Sweden will waive informed consent when using data from national registries for research, which as also was true for our studies. Nevertheless, there are rigorous restrictions as to how and when the retrieved information can be used. We believe that the research benefits both patients and society, and that informed consent should not be required for large-scale medical research. Collecting informed consent could have reduced the statistical power and the costs of obtaining the consent from the controls (the cases were not alive) would be unreasonably large and prohibit this research. The pros and cons with the PIN and registry-based health data with no required informed consent have been discussed in-depth previously [113]. In our study the linkage procedure was performed at the NBHW where the PIN was replaced with a serial number to ensure anonymity. The collected data were handled safely, not shared with others and data will be destroyed once the evaluation has been completed or when it is no longer needed for the project. Our aim was to ensure patient data protection and confidentiality in agreement with the guidelines for Good Practice in Data Privacy, Medical Record Confidentiality, and Research developed by the International Society for Pharmacoepidemiology (ISPE). However, some of the pre-defined variables, e.g. substance abuse, mental disorder or living alone, could be associated with stigma. The aim of the thesis was to identify risk factors for non-adherence; and the data have been handled with caution in order to avoid stigmatisation and avoid putting all the responsibility on the patient. Study II

and III were approved by the Regional Ethics Review Board in Linköping, Sweden; study II: Dnr 2014/11-31 and study III: 2012/343-31 and 2017/328-32.

Ethical considerations of adherence

In medicine and in Swedish healthcare there are four well-established central principles of medical ethics. Ethical discussions are frequently based on these four basic principles which were described by Beauchamp and Childress [183]. They should also be considered when it comes to adherence to treatment.

- The principle of goodness
- The principle of no harm
- The principle of justice
- The principle of autonomy

The principle of goodness and the principle of no harm are important, since adherence will only benefit the patient if the patient initially has been prescribed an adequate treatment regimen. It is important that drugs are thoroughly tested in order to protect patient safety since the treatment should do more good than harm. There is no clear hierarchy between these principles. However, when comparing them, some treatments may be ethically correct in one case but not in another. The principle of justice is that everyone should be cared for equally, which can be an issue if healthcare providers offer adherence support selectively to some subpopulations. On the other hand, it could be fair to offer adherence support to patients who need it the most. The principle of autonomy is obvious, in that a patient cannot be forced to be adherent if the patient actively chooses to be non-adherent or chooses to discontinue the treatment. The communication and collaborative relationship between the diseased and the healthcare provider seems to be very central to making adherence to treatment successful.

Non-adherence to medication is a common problem in healthcare and presents a major barrier to safe, efficient, and effective healthcare delivery. Therefore, it is important to recognise potential risk factors for non-adherence and discuss the ethical and medico-legal problems. Further research is warranted regarding potential solutions to this common problem.

Does a history of non-adherence disqualify individuals for some treatments or could it be used as a diagnostic tool to identify individuals that could benefit from some other treatment regimens or support programs?

11 CONCLUSIONS

11.1 GENERAL

The consequences of inadequate use of GLD in individuals with diabetes mellitus in Sweden are multifaceted. Patients who do not adhere to medication may demonstrate therapeutic failure, experience side-effects, and even result in premature death.

The results in this thesis reveal generally poor glycaemic control in clinical practice in Sweden. Poor glycaemic control is an obvious consequence of inadequate use of GLDs. This thesis indicates that both patient behaviour and the physician's clinical inertia represent crucial barriers to adequate use of glucose-lowering drugs. Our findings suggest there is a need for strategies to detect inadequate use of medication, since non-adherence usually remains unseen. The results also highlight the need for improving adherence to prescribed drugs as well as ensure appropriate prescription of GLD in patients with diabetes.

Overall, the studies indicate that patients with risk factors such as experiences of side-effects, poor refill adherence, and living alone, contraindications for the medicine or with substance abuse seem to be vulnerable groups at increased risk of negative consequences due to inadequate use of GLD.

By linking data from the NFMD with national registries, we generated unique data which were supplemented with information from autopsy reports and police reports, and medical charts, when available, thus allowing for a detailed phenotyping that is not possible to generate from the national registries in isolation. This approach was the basis for the identification of consequences of, and risk factors for, inadequate use of GLD. The results may be used in the preventative work to reduce premature death in persons with diabetes.

11.2 THE SPECIFIC STUDIES IN THIS THESIS

Study I

Symptoms of hypoglycaemia in individuals with T2DM were significantly associated with non-adherence to GLD and with lower scores for patient satisfaction with the GLDs and more barriers for adherence, even with lower mean HbA1c values.

The overall HbA1c goal achievement was poor and there were no differences between the adherent and the non-adherent groups, demonstrating the challenge to achieve glycaemic control without symptoms of hyperglycaemia.

Study II

This study identified several significant risk factors for fatal hyperglycaemia such as insulin treatment, poor glycaemic control, inadequate refill adherence, history of microvascular disease, history of psychiatric illness, substance abuse and living alone. Identified groups could benefit from special attention by clinicians to improve adherence and glycaemic control to reduce the rate of serious hyperglycaemia.

In addition, the results showed that there were a significant number of individuals with undiagnosed diabetes where fatal hyperglycaemia obviously was the first manifestation of the disease, in most cases probably representing a recently developed diabetes, which went undetected because the patient did not seek help, or because suspicion of diabetes were not raised by the symptoms that the patient described upon health care visits. Tests for diabetes are readily available and easy to carry out; these studies suggest that such testing be done more liberally.

Study III

This study showed that elevated drug concentrations may not only be due to an acute high intake but may result from accumulation of metformin due to impaired elimination. Most of the intoxicated subjects had one or more contraindications for the use of metformin suggesting that patients' behaviour and physicians' prescription pattern may both contribute to inadequate use of metformin.

The revealed evidence may lead to more careful administration of metformin to minimize risks in patients with identified risk factors particularly where safer alternative exist.

In Study III we also provide fatal and non-fatal postmortem femoral blood reference concentrations of metformin that is expected to be useful in the evaluation of suspected fatal intoxications, and in obscure cases. The results suggest that metformin intoxication could be considered to be the cause of death when the postmortem femoral blood concentrations exceed 10 microgram/mL.

12 CLINICAL IMPLICATIONS AND FUTURE STUDIES

As the prevalence and complexity of diabetes mellitus increase with population ageing, the demography in Sweden indicates that the role of overall adequate use of medicine, including adherence to medicine and evidence-based prescribing is likely to gain even more importance.

Non-adherence to medication could be considered as a condition that can be modified. However, most healthcare providers are not trained to recognise or handle medication non-adherence. This thesis provides relevant information to healthcare providers that can be used to identify subgroups that may be at risk of serious non-adherence to GLD. The health care systems need to intensify their effort in informing physicians, pharmacists as well as patients to recognise inadequate use of medicine in order to diminish the risk of serious consequences due to inadequate use of GLD. We may also develop and improve tools that facilitate the early detection of inadequate use of medicine by using the pharmacy records and the pharmacists, as dispensers of medicines, as a more prominent role in the future to improve effectiveness of treatment.

Further, the thesis may provide information considered useful for identifying subgroups for targeted actions of future intervention studies, with customised adherence programmes to increase adherence to GLD and improve glycaemic control. In recent years, electronic collection of PROM has become more realistic which may assist the clarification of symptoms, side-effects, and barriers to adherence to medicine to improve the identification of inadequate use of GLD. Further research and implementing strategies of adherence programmes as well as PROMs in clinical practice are warranted.

Future research may focus on decision support tools but also PROMs to adjust the prescription routines and ensure an optimisation of appropriate and effective treatment matched with each patient's preferences for better health outcomes in patients with diabetes mellitus.

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